REMARKS

Claims 24 and 31-54 were pending in the subject application. Applicants have herein amended claim 33. Claims 24 and 31-54 are pending in the subject application

Claim 33 was amended to specify that the 1 to 3 substituents on the R^4 group "are each ... independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$." Support for amended claim 33 can be found in the original specification at, for example, original claim 1.

No new matter is added by this amendment and Applicants respectfully request its entry.

I. Rejection of Claims 24 and 31-54 under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 31-54 under 35 U.S.C. § 112, first paragraph as allegedly being nonenabling for the reasons set forth in the office action. In particular, the Examiner concedes that the specification is "enabling for making pharmaceutically acceptable salts." However the Examiner asserts that it "does not reasonably provide enablement for making solvate or hydrate. The specification does not enable any person skilled in the art to which it pertain, or with which it is most closely associated, to make and use the invention commensurate in scope with these claims." The Examiner attempts to explain his reasoning based on the factors set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Central to the Examiner's argument is his interpretation of the terms "solvate" and "hydrate." In particular, the Examiner equates the terms "solvate" and "hydrate" with "an interstitial solid solution" according to page 358 of West (Solid State Chemistry). According to the Examiner, "[t]he solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced." Based on this *narrow* interpretation of the terms "solvate" and "hydrate," the Examiner states that "in the absence of experimentation one cannot predict if a particular solvent will solvate any predictable crystal. One cannot predict the stoichiometry of the formed solvate, i.e., if one, two, or a half a molecule of solvent added per molecule of host." The Examiner also refers to an article by Vippagunta *et al.*, *Advance Drug Delivery Reviews* 48: 3-26, 2001 to support his position that "formation of hydrates is unpredictable." The Examiner contends that "under experimentation will be required to make Applicants' invention. Applicants traverse this rejection.

As a preliminary matter, the Examiner's analysis did not consider all the

evidence related to each of the Wands' factors, which require that any conclusion of nonenablement must be based on the evidence as a whole. For example, the Examiner alleged that Applicants' disclosure is not sufficient to enable one of ordinary skill in the art to practice "solvate" and "hydrate" because the "numerous examples presented all failed to produce a solvate." Applicants disagree. Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed; "representative [samples] are not required by the statute and are not an end in themselves." *In re Robins*, 429 F.2d 452, 457 (CCPA 1970). Furthermore, the law does not require that everything necessary to practice the invention be disclosed. In fact the Federal Circuit has advised that what is well known is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

Secondly, the Examiner has not given the terms "solvate" and "hydrate" their ordinary meanings. Instead, the Examiner has improperly adopted a narrow definition which takes away from the ordinary and customary meanings of these terms. (See *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1370 (Fed. Cir. 2005 ("Generally claim terms should be construed consistently with their ordinary and customary meanings, as determined by those skilled in the art.").

1. Ordinary meaning of the terms "solvate" and "hydrate"

Dictionary definitions of the terms "solvate" and "hydrate" are not limited to the Examiner's narrow definition of these terms. For example, Stedman's Medical Dictionary defines the term "solvate" as "[a] nonaqueous **solution** or **dispersoid** in which there is a noncovalent or easily reversible combination between solvent and solute, or dispersion means and disperse phase; when water is the solvent or dispersion medium, it is called a hydrate." STEDMAN'S MEDICAL DICTIONARY1634 (Williams & Wilkins 26th Ed. 1995)(attached hereto as Exhibit A-1) (emphasis added). Likewise, Stedman's Medical Dictionary defines the term "hydrate" as "[a] aqueous solvate (in older terminology, a hydroxide); a compound crystallizing with one or more molecules of water; e.g., $CuSO4{\cdot}5H_2O$. *Id.* at 814 (attached hereto as Exhibit A-2).

The Merriam-Webster Online Dictionary similarly defines solvate as "an aggregate that consists of a solute ion or molecule with one or more solvent molecules;

also: a substance (as a hydrate) containing such ions."[1] The Merriam-Webster Online Dictionary defines hydrate as "a compound formed by the union of water with some other substance."[2]

As further explained in an college freshman chemistry textbook in a section relating to dissolution of solids

> Water molecules, being dipoles, are attracted to the surface ions, with the positive ends to the anions and their negative ends to cations. This attractive force between an ion and a polar molecule is called an ion-dipole attraction. It permits the ions to leave the surface of the lattice and become part of the liquid phase. The dissolved ions diffuse through the solution surrounded by their attached water molecules. In this condition, the ions are said to by *hydrated*, and the process of their formation is called *hydration*. (These terms are used when the solvent is water. The more general terms *solvated* and *solvation* are used to indicate the attachment of molecules of any solvent.)

Chemistry, Claude H. Yoder *et al.*, Harcourt Brace Jovanovich, Inc., New York (1975), page 255 (attached hereto as Exhibit B)(emphasis in original).

Still further, in Chapter 2 of *Solvents and Solvent Effects in Organic Chemistry*, Christian Reichert, 3rd Edition, Wiley-VCH (2003) pages 5-56,[3] (attached hereto as Exhibit C), the author states that "[t]he term *solvation* refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules. This solvent shell is the result of intermolecular forces between solute and solvent. For aqueous solutions the term used is *hydration*" (emphasis added). See Exhibit C, page 30 under section heading entitled "2.3 Solvation." The entire text of Exhibit B is replete with the use of the term salvation (and hydration) to describe solutes dissolved in organic solvents (and water).

In summary, and contrary to the Examiner's position, the terms "solvate" and "hydrate" as recited in the claims of the subject application should **not** be limited to an interstitial solid solution having a stoichiometric amount of solvent. Rather, "solvate" and "hydrate" should be given their ordinary and customary meanings to encompass any combination or union of a compound of the invention and a solvent including dissolved compounds (e.g., salt solutions), stoichiometric solids and mixtures, and

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[1] Merriam-Webster Online Dictionary, last visited on March 14, 2007 and available at http://209.161.33.50/dictionary/solvate.

[2] Merriam-Webster Online Dictionary, last visited on March 14, 2007 and available at http://209.161.33.50/dictionary/hydrate.

[3] A copy of Exhibit B is available at http://www3.interscience.wiley.com/cgi-bin/booktext/107628669/BOOKPDFSTART, last visited on March 20, 2007.

nonstoichiometric solids and mixtures. Such ordinary and customary meaning of these terms is entirely consistent with Applicants' use of the terms in the claims and written description of the subject application.

"Absent an express intent to impart a novel meaning, claim terms take on their ordinary meaning." *Eleckt Instrument S.A. v. O.U.R. Sci. Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed. Cir. 2000).

As explained above, the ordinary meanings of the terms "solvate" and "hydrate" encompass any combination of a compound of the invention and a solvent including dissolved compounds (e.g., salt solutions), stoichiometric solids and mixtures, and nonstoichiometric solids and mixtures. And because Applicants did not an express intent to impart a novel meaning, the Examiner **must** give these terms their ordinary and customary meaning as set forth above and as required by *Eleckt Instrument S.A.*

2. Solvates and hydrates can be prepared without undue experimentation

Based on the proper definition of "solvate" and "hydrate" discussed above, Applicants submit that one skilled in the art of synthetic organic chemistry could readily prepare "hydrates" and "solvates" of compounds of the invention without undue experimentation. In fact, based on the teachings of the Yoder reference, dissolution of a salt *necessarily* requires the formation of **solvated** ions (or when water is the solvent, **hydrated** ions). As explained in the Yoder reference, one step in the dissolution process (contacting the solvent with the solid lattice) requires "an attractive force between an ion and a polar molecule [which] is called an ion-dipole attraction. It permits the ions to leave the surface of the lattice and become part of the liquid phase." See Exhibit B, page 255. A more rigorous mathematical approach is presented in the Reichert reference, which describes the solvation energy required to solvate a solute in terms of the Gibbs energy and the coordination of solvent molecules to the solute. See Exhibit B, page 30, last paragraph through page 38, last paragraph before the section heading entitled "2.4 Selective Solvation."

Thus, a solvate or hydrate will form on the surface of a solid crystalline lattice in contact whenever the lattice is in contact with an appropriate solvent. Therefore, there is no requirement that the solid crystalline lattice exist as an "interstial solid solution" as asserted by the Examiner. The Yoder reference also states that the same basic principles for dissolution of salts apply to the dissolution of a molecular solid (i.e., a nonionic

compound), albeit with some modifications due to the nature of the attractive forces (see Exhibit B, page 255).

Therefore, one of skill in the art would understand that solvates and hydrates of the compounds of the invention could be made by contacting a compound of the invention with an appropriate solvent including water. And because the formation of a solvate (or hydrate) is predictable when a compound of the invention is contacted with a solvent (or water), the amount of guidance or direction needed to teach one of skill in the art how to make or use the solvates and hydrates is minimal. Thus, Applicants have provided a fully enabling disclosure as required by *In re Wands*.

In view of the above, Applicants submit that the non-enablement rejection of claims 24 and 31-54 has been overcome, and request that the rejection of claims 24 and 31-54 under U.S.C. § 112, first paragraph be withdrawn.

II. Claim Rejections under 35 U.S.C. §103(a)

Claims 31-54 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 20030171359 ("Dahmann"); and claims 31-54 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Nagarathnam[4] for the reasons set forth in the Office Action. Applicants respectfully traverse these rejections for the reasons set forth below.

A. Claims 31-54 are not Obvious over Dahmann

The Examiner states that "Dahmann et al. teaches several 2,4-subsituted diaminopyrimidine compounds for treating abnormal cell growth, which includes the instant compounds. See pages 1-5, formula I and note the definition of various variable groups R^a, R^b, R^c, R^d and R^e, compounds taught by Dahmann et al. include instant compounds. Especially note with the given definition of R^a, R^b, R^c, R^d and R^e, compounds taught by Dahmann et al. include instant compounds. See entire document for further details. See pages 23-86 for large number of examples of compounds made." The Examiner also states: "Note claims 25-30 are rejected as method of use as Dahmann et al. include breast cancer." (Applicants note that method claims 25-30 were earlier cancelled. We believe that the Examiner is referring to pending method claims 31 and

[4] The Office Action referred to claims 1-23, 31 and 32. However, Applicants note that claims 1-23 were earlier cancelled. Thus, we believe that Examiner is referring to pending claims 33-54, which were first presented in the request for continued examination filed on December 7, 2006.

32.)

The Examiner concedes that "Dahmann et al. differs from the instant claims in exemplifying only limited number of compounds in the genus claims in page 1 of compound of formula I. However, Dahmann et al teaches the equivalency of those compounds taught in pages 23-86 with those generically recited in pages 1-5." Nevertheless, the Examiner states that "Dahmann et al. teaches equivalency of the exemplified compounds with those generically claimed. Thus it would have been obvious to one of skill in the art at the time of the invention was made to make compounds using the teachings of Dahmann et al. and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outlined above."

The Examiner also states "[t]hat one trained in the art can make whatever compounds are embraced in the genus using the teaching of the exemplified compounds and expect the resultant compound to have the use taught therein." The Examiner asserts that "one trained in the art would make compounds of the instant genus based on the exemplified compounds (about 265 compounds out of millions of compounds of the instant genus."

Applicants traverse this rejection.

Amended claim 33 of the subject application is directed to a compound of formula I wherein "R^4 is selected from the group consisting of C_6-C_{10} aryl and 5-10 membered heteroaryl, and wherein said aryl and heteroaryl moieties of the foregoing groups are each substituted by 1 to 3 substituents independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$." Contrary to the Examiner's position, Dahmann does not provide any teaching or suggestion to pick and choose amongst his many embodiments and arrive at the claimed compounds.

First, one of skill in the art would need to consider Dahmann's long list of possible R^b groups (see page 2, paragraph [0029] through page 4, paragraph [0064]); select an aralkyl group (see page 2, paragraph [0029]; choose an embodiment where the aralkyl contains an R^2 and R^3 group on adjacent carbon atoms; and choose an embodiment where the R^2 and R^3 join to form a cyclic group (see page 4, paragraph 54 through paragraph [0064]).

Even if one of skill in the art would find a teaching or suggestion in Dahmann to make a diaminopyrimidine having a fused bicyclic aryl R^b group, the skilled artisan would still need to find a motivation or suggestion to select a C_6-C_{10} aryl or 5-10

membered heteroaryl from Dahmann's long list of possible R^d groups which include cyclic amines formed by the joinder of R^c and R^d (see page 4, paragraph [0065] through page 6); (C_1-C_{16})alkyl substituted by groups defined in subsection (a) through (n) see page 7, paragraph [0110] through page 8, paragraph [0124]); and miscellaneous substituted alkyls, cycloalkyls, heterocycloalkyls, aryls, and heteroaryls (see page 8, paragraph [0125] through page 9, paragraph [0147]).

Lastly , even if one of skill in the art would somehow find a motivation or suggestion in Dahmann to make or use a compound where R^b is a fused bicyclic aryl or heteroaryl and R^d is a C_6-C_{10} aryl or 5-10 membered heteroaryl, the skilled artisan would then need to find a teaching or suggestion to substitute the C_6-C_{10} aryl or 5-10 membered heteroaryl of the R^d group with "1 to 3 substituents independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$" as recited in claim 33 of the subject application.

Applicants estimate that Dahmann discloses over 1000 compounds; none of the disclosed compounds contains and R^d group which is a "C_6-C_{10} aryl or 5-10 membered heteroaryl substituted by 1 to 3 substituents independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$" as recited in amended claim 33 of the subject application. Moreover, nowhere does Dahmann teach or suggest making or using any compound where the R^d group contains a C_6-C_{10} aryl or 5-10 membered heteroaryl substituted by 1 to 3 substituents independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$ as recited in amended claim 33 of the subject application.

In summary, Dahmann provide no teaching, suggestion or motivation pick and choose amongst the myriad of his described embodiments, or modify any of his disclosed compounds, and thereby arrive at a compound where R^1 is fused bicyclic aryl or heteroaryl, **and** said R^d is substituted with "1 to 3 substituents independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$" as recited in amended claim 33 of the subject application.

"[A] proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*,

947 F.2d 488, 493 (Fed. Cir. 1991).

As explained above, Dahmann provides no teaching, suggestion or motivation to make or use a pyrimidine compound where R^1 is bicyclic aryl or heteroaryl, **and** said bicyclic aryl or heteroaryl is substituted with "1 to 3 substituents independently selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$" as recited in amended claim 33 of the subject application. Thus, independent claim 33, compound claims 34-54, and method claims 31-32 that depend directly or indirectly upon claim 33 are not obvious over Dahmann.

In view of the above, Applicants respectfully submit that claims 31-54 are not obvious over Dahmann, and request that the rejection of claims 31-54 under 35 U.S.C. § 103(a) be withdrawn.

C. Claims 31-54 are not Obvious over Nagarathnam

The Examiner states that "Nagarathnam et al. teaches several 2,4-substituted diaminopyrimidine compounds for treating viral infection and cancer, which include instant compounds. See pages 3-10, formula I and note the definition of various variable groups C, R^2 and R^3. Especially note with the given definition of C, R^2 and R^3, compounds taught by Nagarathnam et al. include instant compounds. See entire document for details. See pages 27-87 including Table 1-3 for large number of examples of compounds made." The Examiner further states that "[n]ote claims 25-30 are rejected as method of use of Nagarathnam et al. include breast cancer." (Applicants note that method claims 25-30 were earlier cancelled. We believe that the Examiner is referring to pending method claims 31 and 32.)

The Examiner concedes that "Nagarathnam et al. differs from the instant claims in not exemplifying only all the compounds of the genus claimed in pages 3-10 for compound of formula I." Nevertheless, the Examiner asserts that "Nagarathnam et al. teaches the equivalency of those compounds taught in pages 27-87 with those generically recited in pages 3-10." The Examiner contends that "it would have been obvious to one of having ordinary skill in the art at the time the invention was made to make compounds using the teachings of Nagarathnam et al. and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outlined above." Applicants traverse this rejection.

Nagarathnam relates to a broad genus of pyrimidine derivatives where the C2

and C4 positions of the pyrimidine core are each bonded to a group X, as defined in Nagarathnam. In his broadest embodiment, Nagarathnam describes compounds where X can be NR^1R^6, NR^4R^5 or R^4. As described by Nagarathnam, R^1 is "an optionally substituted fused bicyclic unsaturated ring" (see page 3, lines 12-13); "R^6 is hydrogen or alkyl" (see page 4, line 30); R^4 is "an optionally substituted $Y_{(n)}$-mono-ring group or optionally substituted $Y_{(n)}$-multi-ring group" where "n is 0 or 1 and –Y- is selected from the group consisting of straight- or branched-chain C_2-C_3 alkylenyl and –C(CN)-" (see page 4, lines 1-2 and 5-6); and R^5 is "an optionally substituted $Y_{(n)}$-mono-ring group or optionally substituted $Y_{(n)}$-multi-ring group" where "n is 0 or 1 and –Y- is selected from the group consisting of straight- or branched-chain C_2-C_3 alkylenyl, -N=CH-, and -N=CHCH3" (see page 4, lines 16-17 and 20-22). With regard to R^4, Nagarathnam states that when this group is a "ring" it can be substituted with "-halo, $-COOR^8$, $-COR^8$, -CN, $-OR^8$, -C=O, -NO2, $-NR^8R^9$, $-CONR^8R^9$, $-NR^8COR^9$, $-NR^8COOR^9$, $-NR^8SO_2R^9$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8CONR^9$, $-SR^8$, $-NR^8SO_2$, $-OR^8NR^8R^9$, $-N=CR^8$, and optionally substituted alkyl" (see page 4, lines 7-12).

Nagarathnam exemplifies 375 compounds; however, none of the exemplified compounds contain a substituent selected from the group consisting of SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$" as recited in amended claim 33 of the subject application. Furthermore, nowhere does Nagarthnam provide any teaching or suggestion to modify any of his disclosed compounds and thereby arrive at a compound where the substituent attached to the C4 carbon atom contains an aryl or heteroaryl substituted by a SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$ as recited in amended claim 33 of the subject application. Therefore, even if Nagarathnam includes these substituents in his definition of possible substituents on his R4 group, he provides no motivation to pick and choose these specific groups from among the other described groups.

Where an obviousness rejection is made over a prior art class encompassing, but not disclosing, a claimed species or subgenus, the prior art must provide a suggestion to one of ordinary skill in the art to select the specific variables from the disclosed generic formula and thereby arrive at the claimed compound or subgenus. *In re Baird*, 16 F.3d 380, 382-383 (Fed. Cir. 1994). Characterization of a claimed compound as "similar" or "slightly different" from compounds taught in the prior art does not establish the obviousness of the use of compound that is new and nonobvious, since the mere

chemical possibility that a prior art compound could be modified or does support a finding of obviousness unless the prior art suggested the desirability of such a modification. *In re Ochiai*, 71 F.3d 1565, 1570 (Fed. Cir. 1995).

Because Nagarathnam provides no teaching or suggestion that it is desirable to make or use –Y(n)-mono-ring or –Y(n)-multi-ring groups substituted with either a SR^6, SOR^6, SO_2R^6, $NHSO_2R^6$ and $NR^6SO_2R^6$, one of skill in the art would find no suggestion to select these specific variables from the genus described by Nagarathnam and thereby arrive at the claimed invention. Thus, independent claim 33, compound claims 34-54, and method claims 31-32 that depend directly or indirectly upon claim 33 are not obvious over Nagarthnam.

In view of the above, Applicants respectfully submit that claims 31-54 are not obvious over Nagarathnam, and request that the rejection of claims 31-54 under 35 U.S.C § 103(a) be withdrawn.

III. Double Patenting Rejections

The Examiner rejected claims 24 and 31-54 under the judicially created doctrine of double patenting as allegedly being unpatentable over claims 22-25 of copending Application No. 11/127,676. The Examiner also rejected claims 24 and 31-54 under the judicially created doctrine of double patenting as allegedly being unpatentable over claim 1-27 in copending Application No. 11/124,006.

Applicants will address the non-statutory double-patenting issues raised by the Examiner once the claims of the subject application are otherwise in condition for allowance.

CONCLUSION

No additional fee is believed due in connection with this amendment. However, if any fee is due, the Examiner is authorized to charge the fee to Applicants' Deposit Account No. 16-1445.

If the Examiner wishes to comment or discuss any aspect of this application or response, Applicants' undersigned attorney invites the Examiner to call him at the telephone number provided below.

Respectfully submitted,

Date: March 21, 2007

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Exhibit A-1

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Database design by Lexi-Comp Inc., Hudson, OH
Printed in the United States of America by R.R. Donnelley & Sons Company

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985, 1995
Portuguese 1976, 1995
Spanish 1993

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853-1938.
[Medical dictionary]
Stedman's medical dictionary.--26th ed.
p. cm.
ISBN 0-683-07922-0 REGULAR EDITION
ISBN 0-683-07935-2 DELUXE EDITION
1. Medicine--Dictionaries. I. Title. II. Title: Medical dictionary.
[DNLM: 1. Dictionaries, Medical. W 13 S812m 1995]
R121.S8 1995
610'.3--dc20
DNLM/DLC
for Library of Congress

95 96 97
5 4 5 6 7 8 9 10

of $NaHCO_3$, 1 g of D-glucose, and water to make 1000 ml; used to irrigate the peritoneal cavity, and in laboratory work.

volumetric s. (VS), a s. made by mixing measured volumes of the components

Weigert's iodine s., an iodine-potassium iodide mixture used as a reagent to alter crystal and methyl violet so that they are retained by certain bacteria and fungi.

sol-vate (sol'vāt). A nonaqueous solution or dispersoid in which there is a noncovalent or easily reversible combination between solvent and solute, or dispersion means and disperse phase; when water is the solvent or dispersion medium, it is called a hydrate.

sol-va-tion (sol-vā'shŭn). Noncovalent or easily reversible combination of a solvent with solute, or of a dispersion means with the disperse phase; if the solvent is water, s. is called hydration. S. affects the size of ions in solution; thus Na^+ is much larger in H_2O than in solid NaCl.

sol-vent. A liquid that holds another substance in solution, *i.e.*, dissolves it. [L. *solvens*, prev. p. of *solvo*, to dissolve]

amphiprotic s., a s. capable of acting as an acid or a base; *e.g.*, H_2O, see solvolysis, see solvolysis.

fat s.'s, organic liquids notable for their ability to dissolve lipids; usually, but not always, immiscible in water; *e.g.*, diethyl ether, carbon tetrachloride, see nonpolar s.'s.

nonpolar s.'s, syn **lipid s.'s.**

polar s.'s, s.'s that exhibit polar forces on solutes, due to high dipole moment, wide separation of charges, or tight association; *e.g.*, water, alcohols, acids.

universal s., a substance sought by the alchemists, and claimed by some to have been found, supposedly capable of dissolving all substances; sometimes, in a physiological sense, applied to water.

sol-vol-y-sis (sol-vol'i-sis). The reaction of a dissolved salt with the solvent to form an acid and a base; the (partial) reverse of neutralization. If the solvent is water, an amphiprotic solvent, s. is called hydrolysis.

so-ma (sō'mă). **1.** The axial part of the body, *i.e.*, head, neck, trunk, and tail, excluding the limbs. **2.** All of an organism with the exception of the germ cells. see also body, **3.** The body of a nerve cell, from which axons, dendrites, etc. project. [G. *soma*, body]

so-man (sō'man). Methylphosphonofluoridic acid 1,2,2-trimethylpropyl ester; an extremely potent cholinesterase inhibitor. see also sarin, tabun.

so-mas-the-nia (sō-mas-thē'ne-ă). syn somatasthenia.

somat-. see somato-.

so-ma-tag-no-sia (sō'mă-tag-nō'sē-ă). syn somato-topagnosis. [somat- + G. *a-*, priv. + *gnosis*, recognition]

so-ma-tal-gia (sō-mă-tal'jē-ă). **1.** Pain in the body. **2.** Pain due to organic causes, as opposed to psychogenic pain. [somat- + G. *algos*, pain]

so-ma-tas-the-nia (sō'mă-tas-thē'ne-ă). A condition of chronic physical weakness and fatigability. syn somasthenia. [somat- + G. *asthenia*, weakness]

so-ma-tes-the-sia (sō'mă-tes-thē'zē-ă). Bodily sensation, the conscious awareness of the body. syn somesthesia. [somat- + G *aisthēsis*, sensation]

so-mat-es-the-tic (sō'mat-es-thet'ik). Relating to somatesthesia.

so-mat-ic (sō-mat'ik). **1.** Relating to the soma or trunk, the wall of the body cavity, or the body in general. syn parietal (2). **2.** Relating to or involving the skeleton or skeletal (voluntary) muscle and the innervation of the latter, as distinct from the viscera or visceral (involuntary) muscle and its autonomic) innervation. syn parietal (3). **3.** Relating to the vegetative, as distinguished from the generative, functions. [G. *somatikos*, bodily]

so-mat-i-co-splanch-nic (sō-mat-i-kō-splangk'nik). Relating to the body and the viscera. syn somaticovisceral. [G. *somatikos*, relating to the body, + *splanchnikos*, relating to the viscera]

so-mat-i-co-vis-cer-al (sō-mat-i-kō-vis'er-ăl). syn somatico-splanchnic.

so-ma-tist (sō'mă-tist). One who considers that neuroses and psychoses are manifestations of organic disease.

so-ma-ti-za-tion (sō'mat-i-zā'shŭn). The process by which psychological needs are expressed in physical symptoms; *e.g.*, the expression or conversion into physical symptoms of anxiety, or a wish for marital gain associated with a legal action following and injury, or a related psychological need. see also somatization *disorder*.

somato-, somat-, somatico-. The body, bodily. [G. *soma*, body]

so-ma-to-chrome (sō'mă-tō-krōm). Denoting the group of neurons of nerve cells in which there is an abundance of cytoplasm completely surrounding the nucleus. [somato- + G. *chroma*, color]

so-ma-to-crin-in (sō'mă-tō-krin'in). Hypothalamic growth releasing hormone, GHRH. [somato- + G. *krino*, to secrete, + -in]

so-ma-to-gen-ic (sō'mă-tō-jen'ik). **1.** Originating in the soma or body under the influence of external forces. **2.** Having origin in body cells. [somato- + G. *genesis*, origin]

so-ma-to-lib-er-in (sō'mă-tō-lib'er-in). A decapeptide released by the hypothalamus, which induces the release of human growth hormone (somatotropin). syn growth hormone-releasing factor, somatotropin releasing hormone. [somatotropin + L. *libero*, to free, + -in]

so-ma-tol-o-gy (sō-mă-tol'ō-jē). The science concerned with the study of the body; includes both anatomy and physiology. [somato- + G. *logos*, study]

so-ma-to-mam-mo-tro-pin (sō'mă-tō-mam'ō-trō'pin). A peptide hormone, closely related to somatotropin in its biological properties, produced by the human placenta and by certain neoplasms. [somato- + L. *mamma*, breast, + G. *trope*, a turning, + -in]

human chorionic s. (HCS), syn human placental *lactogen*

so-ma-to-me-din (sō'mă-tō-me'din). S. A is a peptide (MW of about 4,000), synthesized in the liver and probably in the kidney, that is capable of stimulating certain anabolic processes in bone and cartilage, such as synthesis of DNA, RNA, and protein (including chondromucoprotein), and the sulfation of mucopolysaccharides, secretion and/or biological activity of s. is known to be dependent on somatotropin. see also insulin-like growth *factors*, under *factor*. syn sulfation factor. [*somato-*, tropin (*mediator*) + -in]

so-ma-to-me-dins, syn insulin-like growth *factors*, under *factor*.

so-ma-tom-e-try (sō-mă-tom'e-trē). Classification of persons according to body form, and relation of the types to physiologic and psychologic characteristics. [somato- + G. *metron*, measure]

so-ma-to-pa-gus (sō-mă-top'ă-gŭs). Conjoined twins united in their body regions. see conjoined *twins*, under *twin*. [somato- + G. *pagos*, something fixed]

so-ma-to-path-ic (sō'mă-tō-path'ik). Relating to bodily or organic illness, as distinguished from mental (psychologic) disorder. [somato- + G. *pathos*, suffering]

so-ma-top-a-thy (sō-ma-top'ă-thē). Obsolete term for any disease of the body. [somato- + G. *pathos*, suffering]

so-ma-to-phre-nia (sō'mă-tō-frē'ne-ă). A tendency to imagine or exaggerate bodily ills. [somato- + G *phren*, mind]

so-ma-to-plasm (sō'mă-tō-plazm, sō-mat'ō-). Aggregate of all the forms of specialized protoplasm entering into the composition of the body, other than germ plasm. [somato- + G. *plasma*, something formed]

so-ma-to-pleure (sō'mă-tō-plūr). Embryonic layer formed by association of the parietal layer of the lateral plate mesoderm with the ectoderm. [somato- + G *pleura*, side]

so-ma-to-pros-thet-ics (sō'mă-tō-pros-thet'iks). The art and science of prosthetically replacing external parts of the body that are missing or deformed. [somato- + G. *prosthesis*, an addition]

so-ma-to-psy-chic (sō'mă-tō-sī'kik). Relating to the body-mind relationship; the study of the effects of the body upon the mind, as opposed to psychosomatic, which is mind on body. [somato- + G *psychē*, soul]

so-ma-to-psy-cho-sis (sō'mă-tō-sī-kō'sis). An emotional disorder associated with an organic disease. [somato- + G. *psychosis*, an animating]

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Exhibit A-2

STEDMAN'S

26th Edition

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Database design by Lexi-Comp Inc., Hudson, OH
Printed in the United States of America by R.R. Donnelley & Sons Company

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985, 1995
Portuguese 1976, 1995
Spanish 1993

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853-1938.
[Medical dictionary]
Stedman's medical dictionary.--26th ed.
p. cm.
ISBN 0-683-07922-0 REGULAR EDITION
ISBN 0-683-07935-2 DELUXE EDITION
1. Medicine--Dictionaries. I. Title. II. Title: Medical dictionary.
[DNLM: 1. Dictionaries, Medical. W 13 S812m 1995]
R121.S8 1995
610'.3--dc20
DNLM/DLC
for Library of Congress

95 96 97
5 4 5 6 7 8 9 10

stalked h., SYN vesicula *appendiculata* of uterine tube, under *appendix*.

hy·da·tid·i·form (hi-da-tid'i-form) Having the form or appearance of a hydatid.

hy·da·tid·o·cele (hi-da-tid'o-sel) A cystic mass composed of one or more hydatids formed in the scrotum. [hydatid + G. *kēlē*, tumor]

hy·da·ti·do·ma (hi'da-ti-do'ma) A benign neoplasm in which there is prominent formation of hydatids. [hydatid + G. *-oma*, tumor]

hy·da·tid·o·sis (hi'da-ti-do'sis) The morbid state caused by the presence of hydatid cysts.

hy·da·ti·dos·to·my (hi'da-ti-dos'to-me) Surgical evacuation of a hydatid cyst. [hydatid + G. *stoma*, mouth]

Hy·da·tig·e·ra ta·e·ni·ae·for·mis (hi-da-tij'er-a te-ni-e-for'mis) SYN *Taenia taeniaeformis*.

hy·da·toid (hi'da-toyd) **1.** The aqueous humor. **2.** The hyaloid membrane. **3.** Relating to the aqueous humor. **4.** Watery or resembling water. [G. *hydōr hydatos*, water, + *eidos*, resemblance]

Hyde, James N., U.S. dermatologist, 1840–1910. SEE *Hyde disease*.

hyd·no·car·pus oil (hid-no-kar'pus) SYN chaulmoogra oil.

△hydr-, SEE hydro-.

hy·drac·e·tin (hi-drac'e-tin) Pine form of acetylphenylhydrazine.

hy·drad·e·ni·tis (hi'drad-e-ni'tis) SYN hidradenitis.

hy·drad·e·no·ma (hi'drad-e-no'ma) SYN hidradenoma.

hy·dra·gogue (hi'dra-gog) Producing a discharge of watery fluid; denoting a class of cathartics that retain fluids in the intestine and aid in the removal of edematous fluids, e.g., saline cathartics. [hydr- + G. *agōgos*, drawing forth]

hy·dral·a·zine hy·dro·chlo·ride (hi-dral'a-zen) 1-Hydrazinophthalazine hydrochloride; a vasodilating antihypertensive agent.

hy·dral·o·stane (hi-dral'o-stan) $C_{19}H_{32}O_2$. 3,20-Dihydroxy-5β-pregnane-3,20-diol; nucleus of corticoids; reduced at the 4,5 double bond. SYN 4,5α-dihydrocortisol

hy·dra·mi·na·zine tar·trate (hi-dra'mi-na'zen) 2,4-Bis (diethylamino)-6-hydrazino-s-triazine tartrate; an intestinal antispasmodic.

hy·dram·ni·on, hy·dram·ni·os (hi-dram'ne-on, -os) Polyhydramnios; an excessive amount of amniotic fluid. [G. *hydōr*, water, + amnion]

hy·dran·en·ceph·a·ly (hi'dran-en-sef'a-le) Absence of cerebral hemispheres, which have been replaced by fluid-filled sacs, lined by leptomeninges. The skull and its brain cavities are normal. [hydr- + G. *an-* not + *enkephalos*, brain]

hy·drar·gyr·ia, hy·drar·gy·rism (hi-drar-jir'e-a, hi-drar'jir-izm) SYN mercury *poisoning*. [L. *hydrargyrum*, mercury]

hy·drar·gy·rum (hi-drar'ji-rum) SYN mercury. [G. *hydrargyros*, quicksilver, fr. *hydōr*, water + *argyros*, silver]

hy·drar·thro·di·al (hi-drar-thro'de-al) Relating to hydrarthrosis.

hy·drar·thron (hi-drar'thron) SYN hydrarthrosis.

hy·drar·thro·sis (hi-drar-thro'sis) Effusion of a serous fluid into a joint cavity. SYN hydrarthrosis, hydrarthros, hydrops articuli. [hydr- + G. *arthron*, joint]

intermittent h., a disorder characterized by a periodically occurring serous effusion into the cavity of a joint; the articulation may be the seat of a chronic arthritis or may apparently be normal in the intervals of the attacks.

hy·drar·thrus (hi-drar'thrus) SYN hydrarthrosis.

hy·drase (hi'dras) Former name for hydralase.

hy·dras·tine (hi-dras'tin) An alkaloid of hydrastis or isoquinoline chemically related to narceine. As the hydrochloride, was used locally in the treatment of catarrhal inflammation of the mucous membranes, and internally in the treatment of gastric inflammation, as a uterine stimulant, and to check uterine hemorrhage.

hy·dras·ti·nine (hi-dras'ti-nēn) A semisynthetic alkaloid prepared from hydrastine; the hydrochloride has been used in place of hydrastine and as an oxytocic in large doses, it is a powerful depressant of the entire motor tract (motor cortex, nerve, and muscle).

hy·dras·tis (hi-dras'tis) The dried rhizome of *Hydrastis canadensis* (family Ranunculaceae), a native of the eastern U.S., formerly used in the treatment of chronic catarrhal states of the mucous membranes and in metrorrhagia. SYN golden seal, orangeroot, yellow root. [Mod. L. fr. G. *hydōr hydatos*, water, + *draō*, to accomplish]

hy·dra·lase (hi'dra-las) Trivial name applied, together with dehydratase, to certain hydrolyases (EC class 4.2.1) catalyzing hydration (dehydration) e.g., fumarate malate lyase (fumarase) or fumarate hydratase.

hy·drate (hi'drāt) An aqueous solvate (an older terminology), a hydroxylate; a compound crystallizing with one or more molecules of water, e.g. $CuSO_4·5H_2O$.

hy·drat·ed (hi'drat-ed) Combined with water forming a hydrate. SYN hydrous

hy·dra·tion (hi-dra'shun) **1.** Chemically, the addition of water; differentiated from hydrolyses, where the atoms with which water is accompanied by a splitting of the original molecule and the water molecule. SEE also solvation **2.** Clinically, the taking in of water; used commonly in the sense of reduced h. or dehydration.

absolute h., actual water excess as measured by a difference from the normal or from a given water content

hy·dra·zide (hi'dra-zīd) An organic compound of the general formula RCO·NH·NH$_2$; an acid derivative of hydrazine.

hy·dra·zine (hi'dra-zen, -zin) $H_2N·NH_2$, from which phenylhydrazine and similar products are derived.

hy·dra·zine yel·low, SYN tartrazine.

hy·dra·zi·no·yl·sis (hi'dra-zi-no'il-sis) Cleavage of chemical bonds by hydrazine (NH$_2$·NH$_2$) applied in glycan and nucleic acid degradations.

hy·dra·zone (hi'dra-zon) A substance derived from aldehydes and ketones by reaction with hydrazine or a hydrazine derivative to give the grouping >C=N·NH.

hy·dre·mia (hi-dre'me-a) A condition in which the blood volume is increased as a result of an increase in the water content of plasma, with or without a reduction in the concentration of protein; there is an excess of plasma in proportion to the cellular elements, and a corresponding decrease in hematocrit. SYN dilution anemia, polyhydremia. [hydr- + G. *haima*, blood]

hy·dren·ceph·a·lo·cele (hi-dren-sef'a-lo-sel) Protrusion, through a defect in the skull of brain substance expanded into a sac containing fluid. SYN encephalohydrocele, hydroencephalocele, hydromeningocele. [hydr- + G. *enkephalos*, brain, + *kēlē*, tumor]

hy·dren·ceph·a·lo·me·nin·go·cele (hi-dren-sef'a-lo-me-ming'go-sel) Protrusion, through a defect in the skull, of a sac containing meninges, brain substance, and cerebrospinal fluid.

hy·dren·ceph·a·lus (hi-dren-sef'a-lus) Rarely used term for internal *hydrocephalus*. [hydr- + G. *enkephalos*, brain]

hy·dri·at·ric, hy·dri·a·tric (hi-dre-at'rik, -a'trik) Relating to the obsolete use of water to treat or cure disease. SYN hydriatrician (n.). [hydr- + G. *iatrikos*, relating to medicine]

hy·dric (hi'drik) Relating to hydrogen in chemical combination.

hy·dride (hi'drīd) A negatively charged hydrogen (*e.g.*, H$^-$) or a compound of hydrogen in which it assumes a formal negative charge, e.g., sodium borohydride ($NaBH_4$).

hy·drin·dan·tin (hi-drin-dan'tin) The reduced form of ninhydrin.

△hydro-, hydr- **1.** Water, watery. **2.** Containing or combined with hydrogen. **3.** A hydrant. [G. *hydōr*, water]

hy·droa (hi-dro'a) Any bullous eruption. SYN hidroa. [hydro- + G. *ōon*, egg]

h. aestiva'le, SYN h. vacciniforme

h. fe'brile, SYN *herpes* simplex.

h. gestatio'nis, SYN *herpes* gestationis.

h. herpetifor'me, SYN *dermatitis* herpetiformis.

h. puero'rum, SYN h. vacciniforme.

Exhibit B

CLAUDE H. YODER
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Chemistry

HARCOURT BRACE JOVANOVICH, INC.

New York Chicago San Francisco Atlanta

ISBN: 0-15-506465-7
Library of Congress Catalog Card Number: 74-24771

Printed in the United States of America

Illustrations by Eric G. Hieber Associates, Inc.

Photo Credits

Part I Photomicrograph of polyethylene glycol polymers (Carbowax).

Manfred Kage from Peter Arnold

Part II Surface of a liquid in which a sequence of chemical reactions is proceeding in an array of spiral patterns.

Photo by Fritz Goro

Part III Spiral Nebula (Messier 101) in Ursa Major. Photographed with the 200-inch Hale Telescope at Mt. Palomar, California

Courtesy of Mount Wilson and Palomar Observatories

all components have the same physical state, the one present in the greatest amount is called the solvent and the other components are called solutes. Thus, in a solution formed from 20 ml of ethyl alcohol and 500 ml of water, water is the solvent, ethyl alcohol the solute.

Liquid solutions are by far the most common, and we shall deal primarily with these in the discussions that follow.

THE SOLUTION PROCESS

The difference between solutions and heterogeneous mixtures lies in the size of the dispersed particles. In a solution these are individual molecules or ions, whereas in heterogeneous mixtures they are larger aggregates. In order to gain some understanding of how this molecular dispersion comes about, we must examine the solution process on the molecular level.

As an illustration, let us consider the dissolution of a molecular solid (for example, sugar) in a molecular liquid (say, water). Some crystals of the solute are added to the liquid solvent. Three kinds of intermolecular forces must be taken into account in this system. First, there are the intermolecular forces between solute molecules—the forces holding the molecules together in the crystal lattice. Second, there are attractive forces between the molecules of the liquid solvent. Both these types of forces tend to prevent the formation of a solution. The forces within the crystal must be overcome if solute molecules are to leave the crystal and intermingle with the solvent molecules, and the forces between solvent molecules must be overcome if solute molecules are to disperse among the solvent molecules. The third type of force at work in the system is the intermolecular attraction that exists between solute and solvent molecules. This third force tends to counteract the other two and bring about dissolution, and the stronger the attractions between solute and solvent molecules, the more easily the solute-solute and solvent-solvent forces can be overcome. It is the overall balance of these three types of forces that determines how readily the solute will dissolve in a particular solvent. If conditions are favorable for dissolution, the surface molecules leave the crystal, enter the liquid phase, and by diffusion become dispersed among the solvent molecules. The next layer of solute molecules becomes the surface layer, and these in turn enter the liquid phase, and so on, as the crystal dissolves.

The *rate* at which this dissolution occurs (the number of solute molecules entering the liquid phase per unit time) is dependent on the nature of the solute and the solvent, for the strengths of the various intermolecular forces are determined, of course, by the particular structure and composition of the substances involved. For a given solute-solvent system, the rate of solution varies with temperature and the surface area of the solute as follows:

Temperature. An increase in temperature has several effects on the system, all of which combine to *increase* the rate of solution. Higher temperatures increase the kinetic energy of the solute molecules, thus lessening the effectiveness of the

lattice forces. The kinetic energy of the solvent molecules is also increased at higher temperatures, so that solvent-solvent attractions are more easily overcome. Finally, higher temperatures increase the rate with which solute molecules diffuse through the solvent.

Surface area. Since dissolution of a solid solute is a surface phenomenon, the greater the surface area of the solid the higher will be its rate of solution. A pulverized solid will dissolve *faster* than the same substance in one large lump, because pulverization increases the surface area. Stirring or agitation of the mixture will also increase the rate of solution, because this action increases the amount of surface in contact with the liquid. Stirring also aids in diffusion of the dissolved molecules.

As the solution process continues, more and more solute molecules enter the liquid phase. These "dissolved" molecules are in random motion along with the solvent molecules. As a result of this motion, solute molecules in the liquid phase undergo collisions with the surface of the crystal. If a collision occurs when a "dissolved" molecule has a sufficiently low kinetic energy, it may be "captured" by the lattice forces at the surface of the crystal and become part of the crystal again. This process, which is the reverse of dissolution, is called crystallization. Thus we have two opposing processes occurring in the system (illustrated in Figure 11-1) which can be represented by the expression

$$\text{Undissolved solute} \rightleftharpoons \text{Dissolved solute}$$

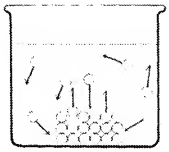

FIGURE 11-1
Dissolution and Crystallization

The *rate* of crystallization is determined by the same factors that determine the rate of solution—nature of solute and solvent, temperature, and surface area of solute—and one additional factor, the number of solute molecules in the liquid phase.

As was indicated above, for a given solute and solvent at a given temperature and with a given surface area, the *rate of solution* is essentially constant with time. The *rate of crystallization*, however, begins at zero and gradually increases because the number of dissolved solute molecules is constantly increasing. Eventually therefore, the rates of the two opposing processes must become equal, and a state of *dynamic equilibrium* is reached. (Note the similarity to the evaporation of a liquid in a closed system, p. 204). In this state, if the temperature is held constant

solute will continue to dissolve and to crystallize at the same rate, and there will be no net change in the *amount* of solute dissolved. A solution in which this situation exists—that is, one in which *the dissolved solute is in equilibrium with the undissolved solute*—is called a *saturated* solution. When a solution contains *less* dissolved solute than the *equilibrium amount* it is said to be *unsaturated*, if it contains *more* than the equilibrium amount it is called *supersaturated* (see p. 259).

Let us now consider the dissolution of an *ionic* solid in a liquid; for example, sodium chloride in water. In general, our discussion of the dissolution of a molecular solid applies also to an ionic solid, with some modifications necessary because of the difference in the nature of the attractive forces.

Recall that an ionic solid consists of positive and negative ions arranged alternately in the crystal lattice and held together by rather strong electrostatic attractions. Ions in the body of the crystal are surrounded by some number of ions of opposite charge and are therefore subjected to attractions in all directions. The electrostatic attractions on the surface ions, however, are unbalanced, and these are the ions that come into contact with the solvent molecules. Water molecules, being dipoles, are attracted to the surface ions, with their positive ends to the anions and their negative ends to the cations. This attractive force between an ion and a polar molecule is called an *ion-dipole attraction*. It permits the ions to leave the surface of the lattice and become part of the liquid phase. The dissolved ions diffuse through the solution surrounded by their attached water molecules. In this condition the ions are said to be *hydrated*, and the process of their formation is called *hydration*. (These terms are used when the solvent is water. The more general terms *solvated* and *solvation* are used to indicate the attachment of molecules of any solvent.) As in the case with molecular solutes, if sufficient solute is present, an equilibrium will be established between the dissolved and undissolved ionic substance, giving a saturated solution.

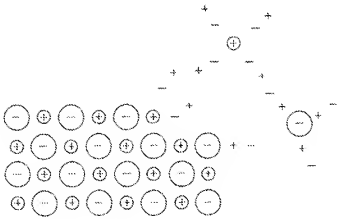

FIGURE 11-2

Dissolution of an Ionic Crystal in Water

Exhibit C

Christian Reichardt

Solvents and Solvent Effects in Organic Chemistry

Third, Updated and Enlarged Edition

WILEY-VCH

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First Reprint 2004

Library of Congress Card No.: applied for

A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at http://dnb.ddb.de.

ISBN 3-527-30618-8

Composition: Asco Typesetters, Hong Kong. Printing: Strauss Offsetdruck GmbH, Mörlenbach
Bookbinding: J. Schäffer GmbH & Co. KG, Grünstadt
Printed in the Federal Republic of Germany.

2 Solute-Solvent Interactions

2.1 Solutions

In a limited sense *solutions* are homogeneous liquid phases consisting of more than one substance in variable ratios, when for convenience one of the substances, which is called the *solvent* and may itself be a mixture, is treated differently from the other substances, which are called *solutes* [1]. Normally, the component which is in excess is called the solvent and the minor component(s) is the solute. When the sum of the mole fractions of the solutes is small compared to unity, the solution is called a *dilute solution*[*]. A solution of solute substances in a solvent is treated as an *ideal dilute solution* when the solute activity coefficients γ are close to unity ($\gamma = 1$) [1, 171]. Solute/solvent mixtures $A + B$ that obey Raoult's law over the entire composition range from pure A to pure B are called *ideal solutions*. According to Raoult, the ratio of the partial pressure of component $A(p_A)$ to its vapour pressure as a pure liquid (p_A^*) is equal to the mole fraction of $A(x_A)$ in the liquid mixture, *i.e.* $x_A = p_A/p_A^*$. Many mixtures obey Raoult's law very well, particularly when the components have a similar molecular structure (*e.g.* benzene and toluene).

A solvent should not be considered a macroscopic continuum characterized only by physical constants such as density, dielectric constant, index of refraction *etc.*, but as a discontinuum which consists of individual, mutually interacting solvent molecules. According to the extent of these interactions, there are solvents with a pronounced internal structure (*e.g.* water) and others in which the interaction between the solvent molecules is small (*e.g.* hydrocarbons). The interactions between species in solvents (and in solutions) are at once too strong to be treated by the laws of the kinetic theory of gases, yet too weak to be treated by the laws of solid-state physics. Thus, the solvent is neither an indifferent medium in which the dissolved material diffuses in order to distribute itself evenly and randomly, nor does it possess an ordered structure resembling a crystal lattice. Nevertheless, the long-distance ordering in a crystal corresponds somewhat to the local ordering in a liquid. Thus, neither of the two possible models – the gas and crystal models – can be applied to solutions without limitation. There is such a wide gulf between the two models in terms of conceivable and experimentally established variants, that it is too difficult to develop a generally valid model for liquids. Due to the complexity of the interactions, the structure of liquids – in contrast to that of gases and solids – is the least-known of all aggregation states. Therefore, the experimental and theoretical examination of the structure of liquids is among the most difficult tasks of physical chemistry [2–7, 172–174].

Any theory of the liquid state has to explain – among others – the following facts: Except for water, the molar volume of a liquid is roughly 10% greater than that of the corresponding solid. According to X-ray diffraction studies, a short-range order of solvent molecules persists in the liquid state and the nearest neighbour distances are almost the same as those in the solid. The solvent molecules are not moving freely, as in the

[*] The superscript ∞ attached to the symbol for a property of a solution denotes the property of an *infinitely dilute solution*.

Solvents and Solvent Effects in Organic Chemistry, Third Edition. Christian Reichardt
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ISBN: 3-527-30618-8

gaseous state, but instead move in the potential field of their neighbours. The potential energy of a liquid is higher than that of its solid by about 10%. Therefore, the heat of fusion is roughly 10% of the heat of sublimation. Each solvent molecule has an environment very much like that of a solid, but some of the nearest neighbours are replaced by holes. Roughly one neighbour molecule in ten is missing.

Even for the most important solvent – water – the investigation of its inner fine structure is still the subject of current research [8–15, 15a]*). Numerous different models, *e.g.* the "flickering cluster model" of Franck and Wen [16], were developed to describe the structure of water. However, all these models prove themselves untenable for a complete description of the physico-chemical properties of water and an interpretation of its anomalies [304]. Fig. 2-1 should make clear the complexity of the inner structure of water.

Liquid water consists both of bound ordered regions of a regular lattice, and regions in which the water molecules are hydrogen-bonded in a random array; it is permeated by monomeric water and interspersed with random holes, lattice vacancies, and cages. There are chains and small polymers as well as bound, free, and trapped water molecules [9, 176]. The currently accepted view of the structure of liquid water treats it as a dynamic three-dimensional hydrogen-bonded network, without a significant number of non-bonded water molecules, that retains several of the structural characteristics of ice (*i.e.* tetrahedral molecular packing with each water molecule hydrogen-bonded to four nearest neighbours), although the strict tetrahedrality is lost [176]. Its dynamic behaviour resembles that of most other liquids, with short rotational and translational correlation times of the order of 0.1 to 10 ps, indicating high hydrogen-bond exchange rates [176, 305].

In principle, other hydrogen-bonded solvents should possess similar complicated structures [306]. However, whereas water has been thoroughly studied [17, 176, 307], the inner structures of other solvents are still less well known [172, 177–179]. By way of example, the intermolecular structure of acetone is determined mainly by steric interactions between the methyl groups and, unexpectedly, only to a small extent by dipole/dipole forces [308], whereas the inner structure of dimethyl sulfoxide is dictated by strong dipole/dipole interactions [309].

From the idea that the solvent only provides an indifferent reaction medium, comes the *Ruggli-Ziegler dilution principle*, long known to the organic chemist. According to this principle, in the case of cyclization reactions, the desired intramolecular reaction will be favoured over the undesired intermolecular reaction by high dilution with an inert solvent [18, 310].

The assumption of forces of interaction between solvent and solute led, on the other hand, to the century-old principle that "like dissolves like" *(similia similibus solvuntur)*, where the word "like" should not be too narrowly interpreted. In many cases, the presence of similar functional groups in the molecules suffices. When a chemical

*) The amusing story of "polywater," which excited the scientific community for a few years during the late 1960's and early 1970's, has been reviewed by Franks [175]. It turned out that polywater was not a new and more stable form of pure water, but merely dirty water. The strange properties of polywater were due to high concentrations of siliceous material dissolved from quartz capillaries in which it was produced.

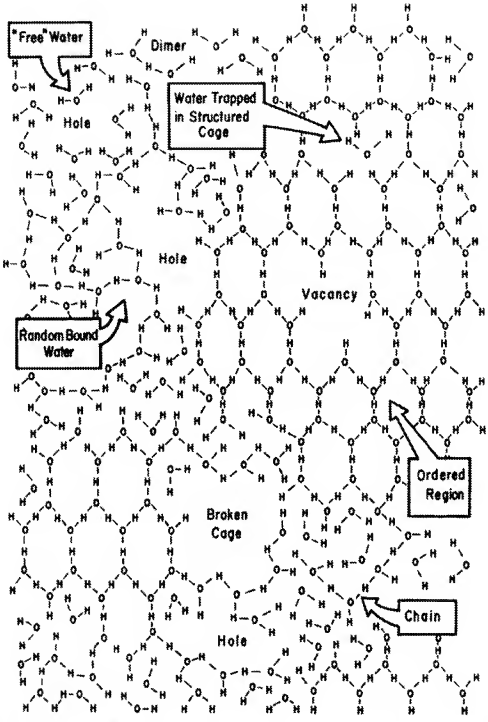


Fig. 2-1. Two-dimensional schematic diagram of the three-dimensional structure of liquid water [9].

similarity is present, the solution of the two components will usually have a structure similar to that of the pure materials (*e.g.* alcohol-water mixtures [19]). This rule of thumb has only limited validity, however, since there are many examples of solutions of chemically dissimilar compounds. For example, methanol and benzene, water and *N*,*N*-dimethylformamide, aniline and diethyl ether, and polystyrene and chloroform, are all completely miscible at room temperature. On the other hand, insolubility can occur in spite of similarity of the two partners. Thus, polyvinyl alcohol does not dissolve in ethanol, acetyl cellulose is insoluble in ethyl acetate, and polyacrylonitrile is insoluble in acrylonitrile [20]. Between these two extremes there is a whole range of possibilities where the two materials dissolve each other to a limited extent. The system water/diethyl ether is such an example. Pure diethyl ether dissolves water to the extent of 15 mg/g at 25 °C, whereas water dissolves diethyl ether to the extent of 60 mg/g. When one of the two solvents is in large excess a homogeneous solution is obtained. Two phases occur when the ratio is beyond the limits of solubility. A more recent example of a reaffirmation of the old "like dissolves like" rule is the differential solubility of fullerene (C_{60}), consisting of a three-dimensional delocalized 60π-electron system, in solvents such as methanol ($s = 0.01$ mg/mL) and 1-chloronaphthalene ($s = 50$ mg/mL) [311].

However, rather than the "like dissolves like" rule, it is the intermolecular interaction between solvent and solute molecules that determines the mutual solubility. A compound *A* dissolves in a solvent *B* only when the intermolecular forces of attraction K_{AA} and K_{BB} for the pure compounds can be overcome by the forces K_{AB} in solution [21].

The sum of the interaction forces between the molecules of solvent and solute can be related to the so-called *polarity*[*] of *A* and *B*. Denoting compounds with large interactions $A \cdots A$ or $B \cdots B$, respectively, as polar, and those with small interactions as nonpolar, four cases allowing a qualitative prediction of solubility can be distinguished (Table 2-1).

An experimental verification of these simple considerations is given by the solubility data in Table 2-2.

Table 2-1. Solubility and polarity [22].

Solute A	Solvent B	Interaction			Solubility of A in B
		A···A	B···B	A···B	
Nonpolar	nonpolar	weak	weak	weak	can be high[a]
Nonpolar	polar	weak	strong	weak	probably low[b]
Polar	nonpolar	strong	weak	weak	probably low[c]
Polar	polar	strong	strong	strong	can be high[a]

[a] Not much change for solute or solvent.
[b] Difficult to break up B···B.
[c] Difficult to break up A···A.

[*] For a more detailed definition of solvent polarity, see Sections 3.2 and 7.1.

Table 2-2. Solubilities of methane, ethane, chloromethane, and dimethyl ether in tetrachloro-methane (nonpolar solvent) and acetone (polar solvent) [22].

Solute	Solute polarity	Solubility/(mol · m^{-3}) at 25 °C	
		in CCl_4	in CH_3COCH_3
CH_4	nonpolar	29	25
CH_3CH_3	nonpolar	220	130
CH_3Cl	polar	1700	2800
CH_3OCH_3	polar	1900	2200

The solubilities of ethane and methane are higher in nonpolar tetrachloromethane, whereas the opposite is true for chloromethane and dimethyl ether. A survey of the reciprocal miscibility of some representative examples of organic solvents is given in Fig. 2-2.

Solubility is commonly defined as the concentration of dissolved solute in a solvent in equilibrium with undissolved solute at a specified temperature and pressure. For a deeper and more detailed understanding of the diverse rules determining the solubility of organic compounds in various solvents, see references [312–316].

The *solubility parameter* δ of Hildebrand [4, 24], as defined in Eq. (2-1), can often be used in estimating the solubility of non-electrolytes in organic solvents.

$$\delta = \left(\frac{\Delta U_v}{V_m}\right)^{1/2} = \left(\frac{\Delta H_v - R \cdot T}{V_m}\right)^{1/2} \tag{2-1}$$

In this equation, V_m is the molar volume of the solvent, and ΔU_v and ΔH_v are the molar energy and the molar enthalpy (heat) of vapourization to a gas of zero pressure,

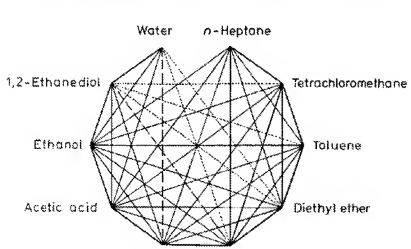


Fig. 2-2. Miscibility of organic solvents [23]. ———— miscible in all proportions; – – – – limited miscibility; ..... little miscibility; without line: immiscible.

respectively. δ is a solvent property which measures the work necessary to separate the solvent molecules (*i.e.* disruption and reorganization of solvent/solvent interactions) to create a suitably sized cavity, large enough to accommodate the solute. Accordingly, highly ordered self-associated solvents exhibit relatively large δ values ($\delta = 0$ for the gas phase). As a rule, it has been found that a good solvent for a certain non-electrolyte has a δ value close to that of the solute [20, 24, 25]; *cf.* Table 3-3 in Section 3.2 for a collection of δ values. Often a mixture of two solvents, one having a δ value higher and the other having a δ value lower than that of the solute is a better solvent than each of the two solvents separately [24]; *cf.* also Section 3.2.

A nice example demonstrating mutual insolubility due to different δ values has been described by Hildebrand [180], and was later improved [181]. A system of eight non-miscible liquid layers was constructed. The eight layers in order of increasing densities are paraffin oil, silicon oil, water, aniline, perfluoro(dimethylcyclohexane), white phosphorus, gallium, and mercury. This system is stable indefinitely at 45 °C; this temperature is required to melt the gallium and phosphorus [181]. A simplified, less harmful version with five colourless liquid phases consists of mineral (paraffin) oil, methyl silicon oil, water, benzyl alcohol, and perfluoro(*N*-ethylpiperidine) (or another perfluoro-organic liquid), in increasing order of density [317]. Addition of an organic-soluble dye can colour some of the five layers.

2.2 Intermolecular Forces [26, 27, 182–184]

Intermolecular forces are those which can occur between closed-shell molecules [26, 27]. These are also called van der Waals forces, since van der Waals recognized them as the reason for the non-ideal behaviour of real gases. Intermolecular forces are usually classified into two distinct categories. The first category comprises the so-called directional, induction, and dispersion forces, which are non-specific and cannot be completely saturated (just as Coulomb forces between ions cannot). The second group consists of hydrogen-bonding forces, and charge-transfer or electron-pair donor–acceptor forces. The latter group are specific, directional forces, which can be saturated and lead to stoichiometric molecular compounds. For the sake of completeness, in the following the Coulomb forces between ions and electrically neutral molecules (with permanent dipole moments) will be considered first, even though they do not belong to the intermolecular forces in the narrower sense.

2.2.1 Ion-Dipole Forces [28, 185]

Electrically neutral molecules with an unsymmetrical charge distribution possess a permanent dipole moment μ. If the magnitude of the two equal and opposite charges of this molecular dipole is denoted by q, and the distance of separation l, the dipole moment is given by $\mu = q \cdot l$. When placed in the electric field resulting from an ion, the dipole will orient itself so that the attractive end (the end with charge opposite to that of the ion) will be directed toward the ion, and the other repulsive end directed away. The potential energy of an ion-dipole interaction is given by

$$U_{\text{ion-dipole}} = -\frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z \cdot e \cdot \mu \cdot \cos\theta}{r^2} \qquad (2\text{-}2)^{*)}$$

where ε_0 is the permittivity of a vacuum, $z \cdot e$ the charge on the ion, r the distance from the ion to the center of the dipole, and θ the dipole angle relative to the line r joining the ion and the center of the dipole. Cos $\theta = 1$ for $\theta = 0°$, *i.e.* in this case the dipole is positioned next to the ion in such a way that the ion and the separated charges of the dipole are linearly arranged ($\overset{+}{\ominus}\!\!-\!\!\overset{-}{\oplus}\ \oplus$ or $\overset{-}{\oplus}\!\!-\!\!\overset{+}{\ominus}\ \ominus$). Equation (2-2) gives the free energy for the interaction of an ionic charge $z \cdot e$ and a so-called 'point-dipole' (for which $l = 0$) in vacuum. For typical interatomic spacings ($r \approx 300$–400 pm), the ion-dipole interaction is much stronger than the thermal energy $k \cdot T$ at 300 K. For the monovalent sodium cation ($z = +1$, radius = 95 pm) near a water molecule (radius ≈ 140 pm; $\mu = 5.9 \cdot 10^{-30}$ Cm), the maximum interaction energy calculated by Eq. (2-2) amounts to $U = 39k \cdot T$ or 96 kJ · mol^{-1} at 300 K [26b].

Only molecules possessing a permanent dipole moment should be called *dipolar molecules*. Apart from a few hydrocarbons (*n*-hexane, cyclohexane, and benzene) and some symmetrical compounds (carbon disulfide, tetrachloromethane, and tetrachloroethene) all common organic solvents possess a permanent dipole moment of between 0 and $18 \cdot 10^{-30}$ Cm (*i.e.* Coulombmeter). Among the solvents listed in the Appendix, Table A-1, hexamethylphosphoric triamide is the one with the highest dipole moment ($\mu = 18.48 \cdot 10^{-30}$ Cm), followed by propylene carbonate ($\mu = 16.7 \cdot 10^{-30}$ Cm), and sulfolane ($\mu = 16.05 \cdot 10^{-30}$ Cm). The largest dipole moments amongst fluids are exhibited by zwitterionic compounds such as the sydnones (*i.e.* 3-alkyl-1,2,3-oxadiazolium-5-olates). For example, 4-ethyl-3-{1-propyl}sydnone, a high-boiling liquid ($t_{bp} = 155$ °C/3 Torr) with a large relative permittivity ($\varepsilon_r = 64.6$ at 25 °C), has a dipole moment of $\mu = 35.7 \cdot 10^{-30}$ Cm (=10.7 D) [318]. The peculiar physical properties of such room temperature liquid sydnones make them to good nonaqueous dipolar solvents for many ionophores (electrolytes).

Ion-dipole forces are important for solutions of ionic compounds in dipolar solvents, where solvated species such as $Na(OH_2)_m^{\oplus}$ and $Cl(H_2O)_n^{\ominus}$ (for solutions of NaCl in H_2O) exist. In the case of some metal ions, these solvated species can be sufficiently stable to be considered as discrete species, such as $[Co(NH_3)_6]^{3\oplus}$ or $Ag(CH_3CN)_{2..4}^{\oplus}$.

For a comprehensive review on ion/solvent interactions, see reference [241].

2.2.2 Dipole-Dipole Forces [29]

Directional forces depend on the electrostatic interaction between molecules possessing a permanent dipole moment μ due to their unsymmetrical charge distribution. When two dipolar molecules are optimally oriented with respect to one another at a distance r as shown in Fig. 2-3a, then the force of attraction is proportional to $1/r^3$. An alternative arrangement is the anti-parallel arrangement of the two dipoles as shown in Fig. 2-3b.

*) It should be noted that Eqs. (2-2) to (2-6) are valid only for gases; an exact application to solutions is not possible. Furthermore, Eqs. (2-2) to (2-6) are restricted to cases with $r \gg l$.

Fig. 2-3. (a) "Head-to-tail" arrangement of two dipole molecules; (b) Antiparallel arrangement of two dipole molecules.

Unless the dipole molecules are very voluminous, the second arrangement is the more stable one. The two situations exist only when the attractive energy is larger than the thermal energies. Therefore, the thermal energy will normally prevent the dipoles from optimal orientation. If all possible orientations were equally probable, that is, the dipoles correspond to freely rotating molecules, then attraction and repulsion would compensate each other. The fact that dipole orientations leading to attraction are statistically favored leads to a net attraction, which is strongly temperature dependent, according to Eq. (2-3) (k_B = Boltzmann constant; T = absolute temperature) [29].

$$U_{\text{dipole-dipole}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{2\mu_1^2 \cdot \mu_2^2}{3k_B \cdot T \cdot r^6} \tag{2-3}$$

As the temperature increases, the angle-averaged dipole/dipole interaction energy becomes less negative until at very high temperatures all dipole orientations are equally populated and the potential energy is zero. This Boltzmann-averaged dipole/dipole interaction is usually referred to as the *orientation* or *Keesom interaction* [29]. According to Eq. (2-3), for pairs of dipolar molecules with $\mu = 3.3 \cdot 10^{-30}$ Cm (=1 D), at a separation of 500 pm, the average interaction energy is about -0.07 kJ · mol^{-1} at 25 °C. This is clearly smaller than the average molar kinetic energy of $3/2\ k \cdot T = 3.7$ kJ · mol^{-1} at the same temperature [26d].

Among other interaction forces, these dipole-dipole interactions are mainly responsible for the association of dipolar organic solvents such as dimethyl sulfoxide [30] or *N*,*N*-dimethylformamide [31].

It should be mentioned that dipoles represent only one possibility for the charge arrays in electric multipoles (*n*-poles). *n-Poles* with an array of point charges with an *n-pole moment* (but no lower moment) are *n-polar*. Thus, a monopole ($n = 1$) is a point charge and a monopole moment represents an overall charge (*e.g.* of an ion Na^+ or Cl^-). A dipole ($n = 2$; *e.g.* H_2O, $H_3C—CO—CH_3$) is an array of partial charges with no monopole moment (*i.e.* no charge). A quadrupolar molecule ($n = 4$; *e.g.* CO_2, C_6H_6) has neither a net charge nor a dipole moment, and an octupolar molecule ($n = 8$; *e.g.* CH_4, CCl_4) has neither charge nor a dipole or quadrupole moment. In addition to dipole/dipole interactions, in solution there can also exist such higher intermolecular multipole/multipole interactions. Therefore, to some degree, octupolar tetrachloromethane is also a kind of polar solvent. However, the intermolecular interaction energy rapidly falls off at higher orders of the multipole [26d]. The anomalous behaviour of the

chair-configured, non-dipolar solvent 1,4-dioxane, which often behaves like a polar solvent even though its relative permittivity is low ($\varepsilon_r = 2.2$), is caused by its large nonideal quadrupolar charge distribution [411].

2.2.3 Dipole-Induced Dipole Forces [32]

The electric dipole of a molecule possessing a permanent dipole moment μ can induce a dipole moment in a neighbouring molecule. This induced moment always lies in the direction of the inducing dipole. Thus, attraction always exists between the two partners, which is independent of temperature. The induced dipole moment*) will be bigger the larger the polarizability α of the apolar molecule experiencing the induction of the permanent dipole. The net dipole/induced dipole energy of interaction for two different molecules, each possessing a permanent dipole moment μ_1 and μ_2 and polarizabilities α_1 and α_2, often referred to as the *induction* or *Debye interaction* [32], is given by Eq. (2-4).

$$U_{\text{dipole-induced dipole}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{\alpha_1 \cdot \mu_2^2 + \alpha_2 \cdot \mu_1^2}{r^6} \tag{2-4}$$

For a dipolar molecule of $\mu = 3.3 \cdot 10^{-30}$ Cm (1 D; *e.g.* H—Cl) separated from a molecule of polarization volume $\alpha = 10 \cdot 10^{-30}$ m^3 (*e.g.* C_6H_6) by a distance of 300 pm, the temperature-independent interaction energy is about -0.8 kJ/mol [26d].

Similarly, a charged particle such as an ion introduced into the neighbourhood of an uncharged, apolar molecule will distort the electron cloud of this molecule in the same way. The polarization of the neutral molecule will depend upon its inherent polarizability α, and on the polarizing field afforded by the ion with charge $z \cdot e$. The energy of such an interaction is given by Eq. (2-5).

$$U_{\text{ion-induced dipole}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{z^2 \cdot e^2 \cdot \alpha}{2 \cdot r^4} \tag{2-5}$$

The importance of both of these interactions is limited to situations such as solutions of dipolar or ionic compounds in nonpolar solvents.

2.2.4 Instantaneous Dipole-Induced Dipole Forces [33, 34, 186]

Even in atoms and molecules possessing no permanent dipole moment, the continuous electronic movement results, at any instant, in a small dipole moment μ, which can fluctuatingly polarize the electron system of the neighbouring atoms or molecules. This coupling causes the electronic movements to be synchronized in such a way that a mutual attraction results. The energy of such so-called *dispersion* or *London* [33] *inter-*

*) The induced dipole moment is defined as $\mu_{\text{ind}} = 4\pi \cdot \varepsilon_0 \cdot \alpha \cdot E$ (ε_0 permittivity of vacuum; α electric polarizability of the molecule; E electric field strength).

actions can be expressed as

$$U_{\text{dispersion}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{3\alpha_1 \cdot \alpha_2}{2r^6} \cdot \left(\frac{I_1 \cdot I_2}{I_1 + I_2}\right) \tag{2-6a}$$

where α_1 and α_2 are the polarizabilities and I_1 and I_2 are the ionization potentials of the two different interacting species [33]. When applied to two molecules of the same substance, Eq. (2-6a) reduces to Eq. (2-6b).

$$U_{\text{dispersion}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{3\alpha^2 \cdot I}{4r^6} \tag{2-6b}$$

Dispersion forces are extremely short-range in action (depending on $1/r^6$!).

Dispersion forces are universal for all atoms and molecules; they alone are responsible for the aggregation of molecules which possess neither free charges nor electric dipole moments. Due to the greater polarizability of π-electrons, especially strong dispersion forces exist between molecules with conjugated π-electron systems (*e.g.* aromatic hydrocarbons). For many other dipole molecules with high polarizability as well, the major part of the cohesion is due to dispersion forces. For example, the calculated cohesion energy of liquid 2-butanone at 40 °C consists of 8% orientational energy, 14% inductional energy, and 78% dispersion energy [35]. Two molecules with $\alpha = 3 \cdot 10^{-30}$ m^3, $I = 20 \cdot 10^{-19}$ J, and $r = 3 \cdot 10^{-10}$ m have an interaction potential of -11.3 kJ/mol (-2.7 kcal/mol) [35a]. These values of α, I, and the average intermolecular distance r correspond to those for liquid HCl. It is instructive to compare the magnitude of these dispersion forces with that of the dipole-dipole interactions. For two dipoles, both with dipole moments of $3.3 \cdot 10^{-30}$ Cm (1.0 D), separated by a distance of $r = 3 \cdot 10^{-10}$ m and oriented as in Fig. 2-3a, the interaction energy is only -5.3 kJ/mol (-1.1 kcal/mol) [35a]. Thus, for HCl and most other compounds, the dispersion forces are considerably stronger than the dipole-dipole forces of nearest neighbour distance in the liquid state. However, at larger distances the dispersion energy falls off rapidly.

As a result of the α^2 term in Eq. (2-6b), dispersion forces increase rapidly with the molecular volume and the number of polarizable electrons. The polarizability α is connected with the molar refraction and the index of refraction, according to the equation of Lorenz-Lorentz. Therefore, solvents with a large index of refraction, and hence large optical polarizability, should be capable of enjoying particularly strong dispersion forces. As indicated in Table A-1 (Appendix), all aromatic compounds possess relatively high indices of refraction, *e.g.* quinoline ($n = 1.6273$), iodobenzene ($n = 1.6200$), aniline ($n = 1.5863$), and diphenyl ether ($n = 1.5763$); of all organic solvents, carbon disulfide ($n = 1.6275$) and diiodomethane ($n = 1.738$) have the highest indices of refraction.

Solvents with high polarizability are often good solvators for anions which also possess high polarizability. This is due to the fact that the dispersional interactions between the solvents and the large, polarizable anions like $I_3^{\ominus}$, $I^{\ominus}$, $SCN^{\ominus}$ or the picrate anion are significantly larger than for the smaller anions like $F^{\ominus}$, $HO^{\ominus}$, or $R_2N^{\ominus}$ [36]. Perfluorohydrocarbons have unusually low boiling points because tightly held electrons in fluorine have only a small polarizability.

2.2.5 Hydrogen Bonding [37–46, 187–190, 306]

Liquids possessing hydroxy groups or other groups with a hydrogen atom bound to an electronegative atom X are strongly associated and have abnormal boiling points. This observation led to the contention that particular intermolecular forces apply here. These are designated as hydrogen bridges, or hydrogen bonds, characterized by a coordinative divalency of the hydrogen atom involved. A general definition of the hydrogen bond is: when a covalently bound hydrogen atom forms a second bond to another atom, the second bond is referred to as a *hydrogen bond* [38].

The concept of hydrogen bonding was introduced in 1919 by Huggins [37]. The first definitive paper on hydrogen bonding – applied to the association of water molecules – was published in 1920 by Latimer and Rodebush [191]. All three were working in the Laboratory of G. N. Lewis, University of California, Berkeley/USA.

A hydrogen bond is formed by the interaction between the partners R—X—H and :Y—R′ according to Eq. (2-7).

$$R\text{-}X\text{-}H \;+\; :Y\text{-}R' \;\rightleftharpoons\; R\text{-}X\text{-}H\cdots Y\text{-}R' \qquad (2\text{-}7)$$

R—X—H is the proton donor and :Y—R′ makes available an electron pair for the bridging bond. Thus, hydrogen bonding can be regarded as a preliminary step in a Brønsted acid-base reaction which would lead to a dipolar reaction product $R—X^{\ominus}\cdots H—Y^{\oplus}—R'$. X and Y are atoms of higher electronegativity than hydrogen (*e.g.* C, N, P, O, S, F, Cl, Br, I). Both inter- and intramolecular hydrogen bonding are possible, the latter when X and Y belong to the same molecule.

The most important electron pair donors (*i.e.* hydrogen bond acceptors) are the oxygen atoms in alcohols, ethers, and carbonyl compounds, as well as nitrogen atoms in amines and *N*-heterocycles. Hydroxy-, amino-, carboxyl-, and amide groups are the most important proton donor groups. Strong hydrogen bonds are formed by the pairs O—H ··· O, O—H ··· N, and N—H ··· O, weaker ones by N—H ··· N, and the weakest by Cl_2C—H ··· O and Cl_2C—H ··· N. The π-electron systems of aromatic compounds, alkenes, and alkynes can also act as weak hydrogen bond acceptors [189].

When two or more molecules of the same type associate, so-called *homo-intermolecular* hydrogen bonds are formed (Fig. 2-4). The association of different molecules (*e.g.* R—O—H ··· NR_3) results in *hetero-intermolecular* hydrogen bonds. The designations *homo-* and *heteromolecular* [192] as well as *homo-* and *heteroconjugated* hydrogen bond are also in use. A remarkable example of a competitive solvent-dependent equilibrium between homo- and hetero-intermolecular hydrogen-bond associated species has been found in solutions of 4-hydroxyacetophenone and 2-(2-hexyloxyethoxy)ethanol [319].

Hydrogen bonds can be either *inter*molecular or *intra*molecular. Both types of hydrogen bonds are found in solutions of 2-nitrophenol, depending on the Lewis basicity of the solvent [298]. The intramolecularly hydrogen-bonded form exists in non-hydrogen-bonding solvents (*e.g.* cyclohexane, tetrachloromethane). 2-Nitrophenol breaks its intramolecular hydrogen bond to form an intermolecular one in electron-pair donor (EPD) solvents (*e.g.* anisole, HMPT).

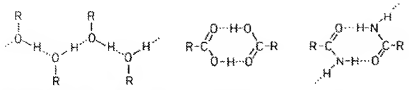
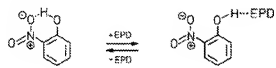


Fig. 2-4. Homo-intermolecular hydrogen bonds in alcohols, carboxylic acids, and amides (the hydrogen bonds are denoted by dotted lines).



Circular hydrogen bonds have been found in the hexahydrate of α-cyclodextrin (cyclohexaamylose) [193]. Hydration water molecules and hydroxy groups of the macromolecule cooperate to form a network-like pattern with circular O—H ··· O hydrogen bonds. If the O—H ··· O hydrogen bonds run in the same direction, the circle is called *homodromic*. Circles with the two counter-running chains are called *antidromic*, and circles with more randomly oriented chains are designated *heterodromic* [193]; *cf.* Fig. 2-4a. Such circular hydrogen bonds can be of importance with respect to the inner molecular structure of water and alcohols (*cf.* also Fig. 2-1).

The question of the exact geometry of hydrogen bonds (distances, angles, lone-pair directionality) has been reviewed [194].

The bond dissociation enthalpy for normal hydrogen bonds is *ca.* 13 ... 42 kJ/mol (3 ... 10 kcal/mol)*). For comparison, covalent single bonds have dissociation enthalpies of 210 ... 420 kJ/mol (50 ... 100 kcal/mol). Thus, hydrogen bonds are approx. ten times weaker than covalent single bonds, but also approx. ten times stronger than the non-

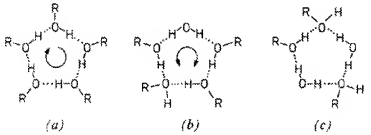


Fig. 2-4a. Three types of circular hydrogen bonds: (a) homodromic, (b) antidromic, and (c) heterodromic hydrogen bonds [193].

*) Bond dissociation enthalpies outside these limits are, however, known. Examples of weak, normal, and strong hydrogen bonds are found in the following pairs: phenol/benzene (ΔH = −5 kJ/mol) [47], phenol/triethylamine (ΔH = −37 kJ/mol) [47], and trichloroacetic acid/triphenylphosphane oxide (ΔH = −67 kJ/mol) [48]. An extremely strong hydrogen bond is found in $Me_4N^+HF_2^-$ (ΔH = −155 kJ/mol) [38]. The strength of a hydrogen bond correlates with the basicity of the proton-acceptor and the acidity of the proton-donor molecule. Compounds with very strong hydrogen bonds have been reviewed [320].

specific intermolecular interaction forces. The question as to whether or not a hydrogen bond is stronger than the equivalent deuterium bond is addressed in reference [321]; the D-bond seems to be somewhat stronger than the H-bond in the case of neutral hydrogen-bonded complexes, but the reverse is true for charged complexes.

Hydrogen bonds are characterized by the following structural and spectroscopic features [39]: (a) the distances between the neighbouring atoms involved in the hydrogen bond [X and Y in Eq. (2-7)] are considerably smaller than the sum of their van der Waals radii; (b) the X—H bond length is increased and hydrogen bond formation causes its IR stretching mode to be shifted towards lower frequencies (for exceptions see reference [190]); (c) the dipolarity of the X—H bond increases on hydrogen bond formation, leading to a larger dipole moment of the complex than expected from vectorial addition of its dipolar components R—X—H and Y—R′; (d) due to the reduced electron density at H-atoms involved in hydrogen bonds, they are deshielded, resulting in substantial downfield shifts of their ^{1}H NMR signals; (e) in hetero-molecular hydrogen bonds, a shift of the Brønsted acid/base equilibrium R—X—H ⋯ Y—R′ ⇌ R—$X^{\ominus}$ ⋯ H—$Y^{\oplus}$—R′ to the right-hand side with increasing solvent polarity is found (*cf.* Section 4.4.1 and references [195, 322] for impressive examples).

Up until now there has been no general agreement as to the best description of the nature of the forces in the hydrogen bond [42–46]. The hydrogen bond can be described as a dipole-dipole or resonance interaction. Since hydrogen bonding occurs only when the hydrogen is bound to an electronegative atom, the first assumption concerning the nature of the hydrogen bond was that it consists of a dipole-dipole interaction such as R—$X^{\delta\ominus}$—$H^{\delta\oplus}$ ⋯ $Y^{\delta\ominus}$—R′. This viewpoint is supported by the fact that the strongest hydrogen bonds are formed in pairs in which the hydrogen is bonded to the most electronegative elements (*e.g.* F—H ⋯ $F^{\ominus}$, $\Delta H = -155$ kJ/mol). The greater strength of the hydrogen bond compared with non-specific dipole-dipole interactions is due to the much smaller size of the hydrogen atom relative to any other atom, which allows it to approach another dipole more closely. This simple dipole model accounts for the usual linear geometry of the hydrogen bond, because a linear arrangement maximizes the attractive forces and minimizes the repulsion.

However, there are reasons to believe that more is involved in hydrogen bonding than simply an exaggerated dipole-dipole interaction. The shortness of hydrogen bonds indicates considerable overlap of van der Waals radii and this should lead to repulsive forces unless otherwise compensated. Also, the existence of symmetrical hydrogen bonds of the type $F^{\delta\ominus} \cdots H \cdots F^{\delta\ominus}$ cannot be explained in terms of the electrostatic model. When the X—Y distance is sufficiently short, an overlap of the orbitals of the X—H bond and the electron pair of :Y can lead to a covalent interaction. According to Eq. (2-8), this situation can be described by two contributing "protomeric" structures, which differ only in the position of the proton*).

$$R\text{-}X\text{-}H\cdots Y\text{-}R' \quad \overset{p}{\longleftrightarrow} \quad R\text{-}X^{\ominus}\cdots H\text{-}Y^{\oplus}\text{-}R' \qquad (2\text{-}8)$$

*) The term "protomeric structure" was obviously introduced in analogy to the well-known "mesomeric structures", which are used to describe the electronic ground state of aromatic compounds such as benzene in terms of a resonance hybrid [323].

The approximate quantum mechanical description of proton states by linear combination of these protomeric structures has been called *protomerism* (symbol *p*) [323, 324]. It seems to be applicable to hydrogen bond systems in which a proton transfer may occur between two potential minima of equal depth [323, 324].

Solvents containing proton-donor groups are designated *protic* solvents [36] or *HBD* solvents [196]; solvents containing proton-acceptor groups are called *HBA* solvents [196]. The abbreviations *HBD* (hydrogen-bond donor) and *HBA* (hydrogen-bond acceptor) refer to donation and acceptance of the proton, and not to the electron pair involved in hydrogen bonding.

Solvents without proton-donor groups have been designated *aprotic* solvents [36]. However, this term is rather misleading, since, for example, solvents commonly referred to as *dipolar aprotic* (*e.g.* CH_3SOCH_3, CH_3CN, CH_3NO_2) are in fact *not* aprotic. In reactions where strong bases are employed, their protic character can be recognized. Therefore, the term *aprotic* solvents should be replaced by *nonhydroxylic* or better still by *non-HBD* solvents [197].

Typical protic or HBD solvents are water, ammonia, alcohols, carboxylic acids, and primary amides. Typical HBA solvents are amines, ethers, ketones, and sulfoxides. *Amphiprotic* solvents can act both as HBD and as HBA solvents simultaneously (*e.g.* water, alcohols, amides; *cf.* Fig. 2-4).

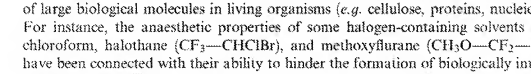
In *type-A* hydrogen bonding, the solute acts as a HBA-base and the solvent as a HBD-acid; in *type-B* hydrogen bonding, the roles are reversed [196].

Hydrogen bonding is responsible for the strong, temperature-dependent self- and hetero-association of amphiprotic solvents (*e.g.* water, alcohols, amides).

The molecular structure of binary HBD/HBA solvent mixtures is largely determined by intermolecular hydrogen bonding between the two components, which usually leads to pronounced deviations from ideal solution behaviour [306, 325–327]. Representative examples are trichloromethane/acetone [326] and trichloromethane/dimethyl sulfoxide mixtures [327], which readily form hydrogen-bonded 1:1 and 2:1 complexes, respectively, with distinct changes in their physical properties as a consequence.

Hydrogen bonding plays a particularly important role in the interactions between anions and HBD solvents. Hence, HBD solvents are good anion solvators. Due to the small size of the hydrogen atom, small anions like $F^{\ominus}$, $Cl^{\ominus}$, or $HO^{\ominus}$ are more effectively solvated by such solvents than the larger ones, *e.g.* $I_3^{\ominus}$, $I^{\ominus}$, $SCN^{\ominus}$, or the picrate ion [36]. This is also one of the reasons why the Gibbs energy of hydration, ΔG_{solv}, of the halide ions decreases in the series $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ [49].

Hydrogen bonding is of paramount importance for the stabilization and the shape of large biological molecules in living organisms (*e.g.* cellulose, proteins, nucleic acids). For instance, the anaesthetic properties of some halogen-containing solvents such as chloroform, halothane (CF_3—$CHClBr$), and methoxyflurane (CH_3O—CF_2—$CHCl_2$) have been connected with their ability to hinder the formation of biologically important hydrogen bonds. This is shown in the following equilibrium [300]:



Halohydrocarbon solvents containing an acidic C—H bond shift this equilibrium in favour of free or less associated species, thus perturbing the ion channels which determine the permeability of neuron membranes to $K^{\oplus}/Na^{\oplus}$ ions in the nervous system. Hydrogen bonds play a decisive role in determining the structure and dimension of these ion channels, on which this permeability depends [300].

Hydrogen-bonding also seems to be the molecular basis of sweetness. All sweet compounds seemingly have a H-bond donor and a H-bond acceptor ca. 250 . . . 400 pm apart, which can form hydrogen bonds with a complementary pair on the sweet receptor in the tastebuds of the tongue [328].

The effectiveness of solvents (and solutes) as hydrogen-bond donors and/or acceptors has been studied experimentally using suitable reference compounds, comprising representative HBDs or HBAs, in order to construct quantitative scales of solvent (and solute) hydrogen-bond acidity and hydrogen-bond basicity, respectively. For reviews on their construction and application to physicochemical and biochemical processes, see references [329–334] as well as Chapter 7. Scales of hydrogen-bond acidity and basicity have mostly been set up using complex formation constants, as determined in inert solvents [329–332]. For example, the strength of HBAs has been measured from the Gibbs energy change ΔG_{HB} for the formation of 1:1 hydrogen-bonded complexes between all kinds of HBAs (bases) and the reference HBD 4-fluorophenol in tetrachloromethane at 25 °C [331, 332]. Other attempts to construct scales of HBD and HBA strengths, *e.g.* the α and β scale of Taft and Kamlet [333, 334], are described in Chapter 7. Not unexpectedly, the pK_{HB} scales derived in this way do not correspond to the common pK_a and pK_b scales, *i.e.* to the normal acidity or basicity constants.

2.2.6 Electron-Pair Donor/Electron-Pair Acceptor Interactions (EPD/EPA Interactions) [50–59, 59a, 59b]

When tetrachloromethane solutions of yellow chloranil and colourless hexamethylbenzene are mixed, an intensely red solution is formed (λ_{max} = 517 nm [50]). This is due to the formation of a complex between the two components, and is only one example of a large number of so-called *electron-pair donor/electron-pair acceptor complexes (EPD/EPA complexes)**). It is generally accepted that the characteristic long-wavelength absorptions of these EPD/EPA complexes are associated with an electron transfer from the donor to the acceptor molecule. Mulliken termed these absorptions "charge-transfer (CT) absorptions" [51].

A necessary condition for the formation of an additional bonding interaction between two valency-saturated molecules is the presence of an occupied molecular

* Synonyms for *EPD/EPA complex* are *electron donor acceptor (EDA) complex* [50], *molecular complex* [57, 58], and *charge-transfer (CT) complex* [51]. Since normally the term *molecular complex* is only used for weak complexes between neutral molecules, and the appearance of a charge-transfer absorption band does not necessarily prove the existence of a stable complex, the more general expression *EPD/EPA complex*, proposed by Gutmann [53], will be used here. This will comprise all complexes whose formation is due to an interaction between electron-pair donors (Lewis bases) and electron-pair acceptors (Lewis acids), irrespective of the stabilities of the complexes or the charges of the components.

orbital of sufficiently high energy in the EPD molecule, and the presence of a sufficiently low unoccupied orbital in the EPA molecule*). Based on the type of orbitals involved in bonding interactions, all EPD molecules can be divided into three groups [51, 53]: *n*-, σ-, and π-EPD. In the first group, the energetically highest orbital is that of the lone pair of *n*-electrons on the heteroatoms (R_2O, R_3N, R_2SO), in the second it is that of the electron pair of a σ-bond (R—Hal, cyclopropane), and in the third it is that of the pair of π electrons of unsaturated and aromatic compounds (alkenes, alkylbenzenes, polycyclic aromatics). Similarly, EPA molecules can also be divided into three groups [51, 53]: *v*-, σ-, and π-EPA. The lowest orbital in the first group is a vacant valency-orbital of a metal atom ($Ag^{\oplus}$, certain organometallic compounds), in the second it is a nonbonding σ-orbital (I_2, Br_2, ICl), and in the third it is a system of π-bonds (aromatic and unsaturated compounds with electron-withdrawing substituents such as aromatic polynitro compounds, halobenzoquinones, tetracyanoethene). Because, in principle, any donor is able to form a complex with any acceptor, there exist nine different types of EPD/EPA complexes. The largest number of investigations have been concerned with complexes of the type π-EPD/π-EPA (*cf.* the above-mentioned hexamethylbenzene/chloranil complex) and π-EPD/σ-EPA (*cf.* complexes of aromatic hydrocarbons and alkenes with halogens and interhalogens).

More recent interesting examples of π-EPD/π-EPA complexes can be found in references [335, 336] and of π-EPD/*v*-EPA complexes (*i.e.* π/cation interactions) in references [337, 338]. For the synthesis of the first free, non-coordinated silyl cation in solution [*i.e.* trimesitylsilylium tetrakis(pentafluorophenyl)borate], the careful selection of a *non-coordinating* solvent, which nevertheless dissolves educts and product, was of crucial importance. Only with arenes as weak EPD solvents, bulky substituents around the silicon atom, and a weak nucleophilic anion, was the synthesis of $(Mes)_3Si^+$ $(F_5C_6)_4B^-$ in solution possible [338].

The reaction enthalpies, ΔH, for the formation of strong EPD/EPA complexes, often used as a measure of the bond energies, lie between −42 and −188 kJ/mol (−10 to −45 kcal/mol) [59]. *n*-EPD/*v*-EPA complexes are particular members of this group (*e.g.* Et_2O—BF_3, $\Delta H = -50$ kJ/mol or −11.9 kcal/mol [60]). For weak complexes, ΔH is usually larger than the dispersion energies but smaller than about 42 kJ/mol (10 kcal/mol) [59]. π-EPD/π-EPA complexes between neutral molecules are examples ($-\Delta H = 0 \ldots 21$ kJ/mol or $0 \ldots 5$ kcal/mol), *e.g.* benzene/1,3,5-trinitrobenzene ($\Delta H = -8$ kJ/mol or −1.9 kcal/mol [57]).

No general agreement exists as to the relative importance of the different intermolecular forces in making up the EPD/EPA complexes. According to Mulliken's VB description of weak EPD/EPA complexes, the electronic ground state can be considered as a hybrid of two limiting structures (*a*) and (*b*) in Fig. 2-5.

The non-ionic structure (*a*) represents a state without any donor-acceptor interactions, in which only non-specific intermolecular forces hold D and A together. The mesomeric structure (*b*) characterizes a state in which an ionic bond has been formed by

*) The fundamental difference between this EPD/EPA bonding interaction and a normal chemical bond is that in an ordinary chemical bond each atom supplies one electron to the bond, whereas in EPD/EPA bonding one molecule (the donor) supplies the pair of electrons, while the second molecule (the acceptor) provides the vacant molecular orbital.

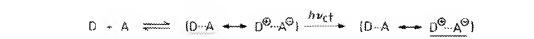
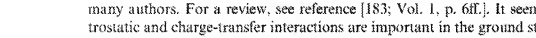


Fig. 2-5. Formation and optical excitation of an EPD/EPA complex between donor D and acceptor A (the predominating mesomeric structure in the ground and excited states is underlined).

transfer of an electron from D to A. This electron transfer will be easier the lower the ionization potential of the donor [61, 63], and the higher the electron affinity of the acceptor [62, 63]. The ionic limiting structure (*b*) is relatively energy-rich and contributes only slightly to the ground state. Nevertheless, this small contribution is sufficient in establishing an extra bonding interaction in addition to the non-specific van der Waals forces. However, subsequent investigations showed that these charge-transfer forces are weaker than was previously believed, and that the classical van der Waals forces (including electrostatic forces) suffice in explaining the stabilities of EPD/EPA complexes [59, 64, 198]. The relative importance of contributions from the electrostatic and charge-transfer forces in the ground state of EPD/EPA complexes has been studied by many authors. For a review, see reference [183; Vol. 1, p. 6ff.]. It seems that both electrostatic and charge-transfer interactions are important in the ground state of EPD/EPA complexes. Their relative contribution, however, varies widely in different EPD/EPA complexes [183].

Another description of EPD/EPA interactions, particularly useful for strong complexes, is based on the coordinative interaction between Lewis bases or nucleophiles (as EPD) and Lewis acids or electrophiles (as EPA) [53, 58]. The intermolecular bonding is seen not as a hybrid of electrostatic and charge-transfer forces, but as one of electrostatic and covalent ones. The interaction of the acceptor A with the electron pair of the donor D is a result of an overlap of the orbitals of the two molecules; consequently, a finite electron density is created between the two partners according to Eq. (2-9).



(2-9)

Hence, the structure $D^{\oplus}\cdots A^{\ominus}$ is a covalent one and the EPD/EPA interaction between D and A can be described as a Lewis acid/base interaction [65].

Of the solvents, aromatic and olefinic hydrocarbons are π-donors (π-EPD); alcohols, ethers, amines, carboxamides, nitriles, ketones, sulfoxides and *N*- and *P*-oxides are *n*-donors (*n*-EPD), and haloalkanes are σ-donors (σ-EPD). Boron and antimony trihalides are acceptor solvents (*v*-EPA), as are halogens and mixed halogens (σ-EPA), and liquid sulfur dioxide (π-EPA). In principle, all solvents are amphoteric in this respect, *i.e.* they may act as a donor (nucleophile) and an acceptor (electrophile) simultaneously. For example, water can act as a donor (by means of the oxygen atom) as well as as an acceptor (by forming hydrogen bonds). This is one of the reasons for the exceptional importance of water as a solvent.

n-Donor solvents are particularly important for the solvation of cations. Examples are hexamethylphosphoric triamide, pyridine, dimethyl sulfoxide, *N,N*-dimethylformamide, acetone, methanol, and water. Their specific EPD properties make them excellent cation solvators, and they are, therefore, good solvents for salts. They are

also known as *coordinating solvents* [66]. The majority of inorganic reactions are carried out in coordinating solvents.

An empirical semiquantitative measure of the nucleophilic properties of EPD solvents is provided by the so-called *donor number DN* (or *donicity*) of Gutmann [53, 67] (*cf.* also Section 7.2). This donor number has been defined as the negative ΔH values for 1:1 adduct formation between antimony pentachloride and electron-pair donor solvents (D) in dilute solution in the non-coordinating solvent 1,2-dichloroethane, according to Eq. (2-10)*.

$$D: + SbCl_5 \xrightarrow[\text{in Cl-CH}_2\text{CH}_2\text{-Cl}]{\text{room temp.}} \overset{\oplus}{D}—\overset{\ominus}{SbCl_5} \qquad (2\text{-}10)$$

Solvent Donor Number $DN = -\Delta H_{D\text{-}SbCl_5}/(\text{kcal} \cdot \text{mol}^{-1})$

The linear relationship between $-\Delta H_{D\text{-}SbCl_5}$ and the logarithm of the corresponding equilibrium constant ($\lg K_{D\text{-}SbCl_5}$) shows that the entropy contributions are equal for all the studied acceptor/donor solvent reactions. Therefore, one is justified in considering the donor numbers as semiquantitative expressions for the degree of coordination interaction between EPD solvents and antimony pentachloride. Antimony pentachloride is regarded as an acceptor on the borderline between hard and soft Lewis acids. A list of organic solvents ordered according to increasing donicity is given in Table 2-3. From this it is seen that, for example, nitromethane and acetonitrile are weak donor solvents, whereas dimethyl sulfoxide and triethylamine are very strong donors. The higher the donor number, the stronger the interaction between solvent and acceptor.

Unfortunately, donor numbers have been defined in the non-SI unit kcal · mol^{-1}. Marcus has presented a scale of dimensionless, normalized donor numbers DN^N, which are defined according to $DN^N = DN/(38.8 \text{ kcal} \cdot \text{mol}^{-1})$ [200]. The non-donor solvent 1,2-dichloroethane ($DN = DN^N = 0.0$) and the strong donor solvent hexamethylphosphoric triamide (HMPT: $DN = 38.8$ kcal · mol^{-1}; $DN^N = 1.0$) have been used to define the scale. Although solvents with higher donicity than HMPT are known (*cf.* Table 2-3), it is expedient to choose the solvent with the highest directly (*i.e.* calorimetrically) determined *DN* value so far as the second reference solvent [200]**. The DN^N values are included in Table 2-3.

A visual estimate of the different donicities of EPD solvents can easily be made using the colour reaction with copper(II), nickel(II), or vanadyl(IV) complexes as acceptor solutes [204].

The donor number has proven very useful in coordination chemistry, since it can be correlated with other physical observables for such reactions, *e.g.* thermodynamic

* An analogous approach was first used by Lindqvist and Zackrisson [67a]. The authors established a series of EPD solvents calorimetrically, based on their increasing donor capacities relative to a standard acceptor ($SbCl_5$ or $SnCl_4$) with which the given donor was combined in 1,2-dichloroethane.

** The donor number of 38.8 kcal · mol^{-1} for HMPT was given by Gutmann [67]. It should be mentioned, however, that a much higher *DN* value of 50.3 kcal · mol^{-1} was subsequently measured for this solvent by Bollinger *et al.* [214]. This shows that serious problems arise in measuring the Lewis basicity of this EPD solvent towards $SbCl_5$.

Table 2-3. Donor numbers (donicities) *DN* [199, 200, 212, 241, 339] and normalized DN^N values [200] of a selection of thirty-six organic EPD solvents[a], determined calorimetrically in dilute 1,2-dichloroethane solutions at room temperature and valid for isolated EPD solvent molecules[b].

Solvents	*DN*/(kcal · mol^{-1})[c]	$DN^{N,d)}$
1,2-Dichloroethane *(reference solvent)*	*0.0*[e]	*0.00*[e]
Nitromethane	2.7	0.07
Nitrobenzene	4.4	0.11
Acetic anhydride	10.5	0.27
Cyanobenzene, Benzonitrile	11.9	0.31
Ethanenitrile, Acetonitrile	14.1	0.36
Tetrahydrothiophene-1,1-dioxide, Sulfolane	14.8	0.38
1,4-Dioxane	14.8	0.38
4-Methyl-1,3-dioxol-2-one, Propylene carbonate	15.1	0.39
(Cyanomethyl)benzene, Benzylcyanide	15.1	0.39
2-Methylpropanenitrile, *i*-Butanenitrile	15.4	0.40
Diethyl carbonate	16.0	0.41
Propanenitrile	16.1	0.41
Methyl acetate	16.3	0.42
1,3-Dioxol-2-one, Ethylene carbonate	16.4	0.42
Butanenitrile	16.6	0.43
3,3-Dimethyl-2-butanone, *t*-Butyl methyl ketone	17.0	0.44
Acetone	17.0	0.44
Ethyl acetate	17.1	0.44
3-Methyl-2-butanone, Methyl *i*-propyl ketone	17.1	0.44
2-Butanone	17.4	0.45
Diethyl ether	19.2	0.49
Tetrahydrofuran	20.0	0.52
Trimethyl phosphate	23.0	0.59
Tri-*n*-butyl phosphate	23.7	0.61
N,N-Dimethylformamide	26.6	0.69
1-Methylpyrrolidin-2-one	27.3	0.70
N,N-Dimethylacetamide	27.8	0.72
Tetramethylurea	29.6	0.76
Dimethyl sulfoxide	29.8	0.77
N,N-Diethylformamide	30.9	0.80
N,N-Diethylacetamide	32.2	0.83
Pyridine	33.1	0.85
Hexamethylphosphoric triamide	38.8	*1.00*[f]
Triethylamine	61.0	1.57

[a] A compilation of 170 resp. 134 *DN*-values taken from different sources can be found in references [200, 339]. Further 14 *DN* values, determined indirectly from the ^{1}H NMR shift of chloroform, are given in reference [293].

[b] As the basic donor numbers were measured in an inert diluent, they reflect the donicity of the isolated EPD solvent molecules. In neat, associated EPD solvents an increase in the donicity should occur [199]. For such highly-structured solvents (*e.g.* water, alcohols, amines) the term *bulk donicity* has been introduced [201] in order to rationalize the deviations of these solvents in plots of ^{23}Na NMR shifts [202] and ESR parameters [203] *vs.* the donor numbers. Because of the great discrepancies which exist between the DN_{bulk} values given in the literature, they are not included in this table. For a collection of bulk donicities, DN_{bulk}, see reference [200], Table II.

[c] For the definition of *DN* *cf.* Eq. (2-10). For conversion into SI units: 1 kcal · mol^{-1} = 4.184 kJ · mol^{-1}.

[d] $DN^N = DN/(38.8 \text{ kcal} \cdot \text{mol}^{-1})$ [200]; *DN* = 38.8 kcal · mol^{-1} for hexamethylphosphoric triamide as reference solvent.

[e] Zero by definition.

[f] Unity by definition [200].

(ΔG or K), kinetic (rates), electrochemical (polarographic half-wave and redox potentials), and spectroscopic data (chemical shifts of NMR signals) [53, 67–69, 205–207].

The donor number approach has been criticized for conceptual [208] and experimental reasons [200, 209–212]. For this and other reasons, other Lewis basicity parameters have been sought.

Another remarkable Lewis basicity scale for 75 non-HBD solvents has been established by Gal and Maria [211, 212]. This involved very precise calorimetric measurements of the standard molar enthalpies of 1:1 adduct formation of EPD solvents with gaseous boron trifluoride, $\Delta H^{\circ}_{D\cdots BF_3}$, in dilute dichloromethane solution at 25 °C, according to Eq. (2-10a).

$$D: + BF_3 \xrightleftharpoons[\text{in } CH_2Cl_2]{25\ ^{\circ}C} \overset{\oplus}{D}\!-\!\overset{\ominus}{B}F_3 \qquad (2\text{-}10a)$$

A selection of $\Delta H^{\circ}_{D\cdots BF_3}$ values is given in Table 2-4. This new Lewis basicity scale is more comprehensive and seems to be more reliable than the donor number scale. A comparison of various Lewis basicity scales has been given by Persson [301].

Persson, Sandström, and Goggin have proposed an empirical solvent scale, called the D_S scale, ranking the donor strength of 64 EPD solvents towards a soft acceptor

Table 2-4. Molar enthalpies of complex formation between boron trifluoride and several non-HBD solvents, determined in dichloromethane at 25 °C, according to Eq. (2-10a) [211, 212].

Solvents	$-\Delta H^{\circ}_{D\cdots BF_3}/(kJ \cdot mol^{-1})$[a]
Dichloromethane	10.0
Nitrobenzene	35.79
Nitromethane	37.63
Tetrahydrothiophene-1,1-dioxide	51.32
Acetonitrile	60.39
Propylene carbonate	64.19
3-Pentanone	72.28
1,4-Dioxane	74.09
Ethyl acetate	75.55
Acetone	76.03
Di-*i*-propyl ether	76.61
Diethyl ether	78.77
Tetrahydrofuran	90.40
1,3-Dimethylimidazolidin-2-one, DMEU	98.93
Dimethyl sulfoxide	105.34
N,N,N',N'-Tetramethylurea	108.62
N,N-Dimethylformamide	110.49
3,4,5,6-Tetrahydro-1,3-dimethylpyrimidin-2(1 *H*)-one, DMPU	112.13
1-Methylpyrrolidin-2-one	112.56
Hexamethylphosphoric triamide	117.53
Tris(pyrrolidino)phosphane oxide	122.52
Pyridine	128.08
Triethylamine	135.87
1-Methylpyrrolidine	139.51

[a] See reference [212] for a set of 75 $\Delta H^{\circ}_{D\cdots BF_3}$ values. At present, $\Delta H^{\circ}_{D\cdots BF_3}$ values for *ca.* 350 organic EPD compounds are known (J.-F. Gal and P.-C. Maria, private communication).

such as mercury(II) bromide [303]. The D_S values correspond to the Raman wavenumber shift of the symmetric IR stretching vibration on going from the gas phase to a solution of $HgBr_2$. Further measurements of $\Delta\nu$(Hg—Br) of $HgBr_2$ and the relationships between the corresponding D_S values and other soft EPD solvent parameters can be found in reference [340]. An additional D_H scale of donor strength towards hard acceptors (*e.g.* $Na^{\oplus}$) has been derived for 24 EPD solvents [303].

An analogous empirical quantity for characterizing the electrophilic properties of EPA solvents has been derived by Gutmann and coworkers from the ^{31}P NMR chemical shifts produced by the electrophilic actions of acceptor solvents A in triethylphosphane oxide, according to Eq. (2-11) (*cf.* also Section 7.4) [70, 199, 207, 213].

$$Et_3P{=}O \longleftrightarrow Et_3\overset{\oplus}{P}-\overset{\ominus}{O}) + A \rightleftharpoons Et_3\overset{\delta\oplus}{P}{=}\overset{\delta\ominus}{O}-A \qquad (2\text{-}11)$$

$$AN = \frac{\ddot{o}_{corr}(A) - \ddot{o}_{corr}(n\text{-}C_6H_{14})}{\ddot{o}_{corr}(Et_3PO{-}SbCl_5) - \ddot{o}_{corr}(n\text{-}C_6H_{14})} \cdot 100 = \Delta\ddot{o}_{corr} \cdot 2.348/\text{ppm}$$

These quantities have been termed *acceptor number AN* (or *acceptivity*) and they were obtained from the relative ^{31}P NMR chemical shift values $\ddot{o}_{corr}$ (*n*-hexane as reference solvent) with respect to that of the 1:1 adduct $Et_3PO{-}SbCl_5$ dissolved in 1,2-dichloroethane, which has been arbitrarily taken to have the value of 100. The acceptor numbers are dimensionless numbers expressing the acceptor property of a given solvent relative to those of $SbCl_5$, which is also the reference compound for assessing the donor numbers. A compilation of organic solvents in order of increasing acceptor number is given in Table 2-5.

Acceptor numbers are less than 10 for nonpolar non-HBD solvents, they vary between about 10...20 for dipolar non-HBD solvents, and they cover a wide range of about 25...105 for protic solvents (*cf.* Table 2-5). Surprisingly, benzene and tetrachloromethane have stronger electrophilic properties than diethyl ether and tetrahydrofuran. Acceptor numbers are also known for binary solvent mixtures [70, 213].

Using the neutral Fe(II) complex $[Fe(phen)_2(CN)_2]$, the different Lewis acidities of EPA solvents can easily be visualized by its colour change: solutions of this Fe(II) complex are blue in HMPT, violet in dichloromethane, red in ethanol, and yellow in trifluoroacetic acid [204].

Another approach to the estimation of EPD/EPA interactions between a Lewis acid A and a Lewis base B was given by Drago [71]. Drago proposed the four-parameter Eq. (2-12) to correlate the standard enthalpy of the reaction of an acceptor A with a donor B to give a neutral 1:1 adduct in an inert solvent (tetrachloromethane or *n*-hexane).

$$-\Delta H^{\circ}_{AB}/(\text{kJ} \cdot \text{mol}^{-1}) = E_A \cdot E_B + C_A \cdot C_B \qquad (2\text{-}12)$$

E_A and C_A are empirical acceptor parameters and E_B and C_B are empirical donor parameters. The E parameters are measures of the tendency of an acid or a base to participate in electrostatic interactions, while the C parameters are measures of their tendency to form covalent bonds.

Table 2-5. Acceptor numbers (acceptivities) *AN* [70, 213, 339] of forty-eight organic EPA solvents, determined ^{31}P-NMR spectroscopically at 25 °C.

Solvents	*AN*[a]
n-Hexane *(reference solvent)*	*0.0*
Triethylamine	1.4
Diethyl ether	3.9
Tetrahydrofuran	8.0
Benzene	8.2
Tetrachloromethane	8.6
Ethyl acetate	9.3
Diethylamine	9.4
Hexamethylphosphoric acid triamide	9.8
Tri-*n*-butyl phosphate	9.9
Diethylene glycol dimethyl ether	9.9
1,2-Dimethoxyethane	10.2
Methyl acetate	10.7
1,4-Dioxane	10.8
Acetone	12.5
1-Methylpyrrolidin-2-one	13.3
N,N-Dimethylacetamide	13.6
Pyridine	14.2
Nitrobenzene	14.8
Cyanobenzene	15.5
N,N-Dimethylformamide	16.0
Trimethyl phosphate	16.3
1,2-Dichloroethane	16.7
4-Butyrolactone	17.3
Morpholine	17.5
4-Methyl-1,3-dioxol-2-one, Propylene carbonate	18.3
N,N-Dimethylthioformamide	18.8
Ethanenitrile, Acetonitrile	18.9
Tetrahydrothiophene-1,1-dioxide, Sulfolane	19.2
Dimethyl sulfoxide	19.3
Dichloromethane	20.4
Nitromethane	20.5
1,2-Diaminoethane	20.9
Chloroform	23.1
2-Methyl-2-propanol, *t*-Butanol	27.1
N-Methylformamide	32.1
1-Butanol	32.2
2-Propanol	33.5
1-Propanol	33.7
2-Aminoethanol	33.7
Ethanol	37.1
Formamide	39.8
Methanol	41.5
Acetic acid	52.9
2,2,2-Trifluoroethanol	53.8
Water	54.8
Formic acid	83.6
$Et_3PO \cdot SbCl_5$ *in 1,2-dichloroethane as reference compound*	*100.0*
Trifluoroacetic acid	105.3

[a] For the definition of *AN*, see Eq. (2-11). All δ values have been extrapolated to zero concentration and corrected for differences in volume susceptibilities.

Table 2-6. Some E and C parameters expressing Lewis acid/base strength according to Drago [217][a]; *cf.* Eq. (2-12).

Lewis acids	E_A	C_A	Lewis bases	E_B	C_B
$SbCl_5$	14.4[b]	1.17[b]	$[(CH_3)_2N]_3PO$	1.52	3.55
BF_3 (g)	9.88	1.62	CH_3SOCH_3	1.34	2.85
$(CF_3)_2CHOH$	5.93	0.62	$CH_3CON(CH_3)_2$	*1.32*[c]	2.58
C_6H_5OH	4.33	0.42	C_5H_5N	1.17	6.40
CF_3CH_2OH	3.88	0.45	$CH_3CO_2C_2H_5$	0.975	1.74
$CHCl_3$	3.02	0.16	CH_3COCH_3	0.94	2.33
$(CH_3)_3C—OH$	2.04	0.30	$(C_2H_5)_2O$	0.94	3.25
H_2O	1.64	0.57	CH_3CN	0.89	1.34
I_2	*1.00*[c]	*1.00*[c]	$(C_2H_5)_2S$	0.34	*7.40*[c]
SO_2	0.92	0.81	C_6H_6	0.28	0.59

[a] For a more complete list see references [71, 215, 217].
[b] Corrected values; see reference [217].
[c] Used to define the E/C scale.

The original set of E and C parameters was determined mainly with the help of enthalpies of adduct formation of iodine and phenol as acceptors with alkylamines as donors. Subsequently, the best set of E and C parameters has been obtained by computer optimization of a large data base of enthalpies and four arbitrarily fixed reference values [71, 215]: $E_A = C_A = 1$ for iodine, $E_B = 1.32$ for *N*,*N*-dimethylacetamide, and $C_B = 7.40$ for diethyl sulfane. Table 2-6 gives a selection of E and C parameters for Lewis acids and bases commonly used as solvents.

On the basis of these parameters, it is possible to predict the enthalpies of Lewis acid/base reactions, even those reactions which might be inaccessible experimentally, with remarkable accuracy (within ± 0.8 kJ $\cdot$ mol^{-1}) [216].

Drago's E/C analysis and Gutmann's donor/acceptor approach [53, 67] have been compared [200, 217, 218]. Eq. (2-12) has been extended for specific and nonspecific interactions between solutes and polar solvents [219]. Various Lewis acidity and basicity scales for polar solvents have been examined and compared by Fawcett, who concluded that the donor/acceptor scales of Gutmann seem to be the most appropriate [341].

Finally, an attempt was made to establish a measure of the electron-donating and electron-accepting power of organic solvents by means of infrared [72, 73] and ^{1}H NMR measurements [73]. Further empirical Lewis acid and base parameters will be discussed in Chapters 7.2...7.5. A thorough and critical compilation of empirical solvent scales, including Lewis acidity and basicity scales, has recently been made for non-HBD solvents [342].

2.2.7 Solvophobic Interactions [74–77, 176, 220–225]

Hydrocarbons have extremely low solubilities in water. Accordingly, the dissolution of a hydrocarbon in water is usually associated with an increase in the Gibbs energy G of the system ($\Delta G > 0$). Since it is known experimentally that the dissolution of a hydrocarbon

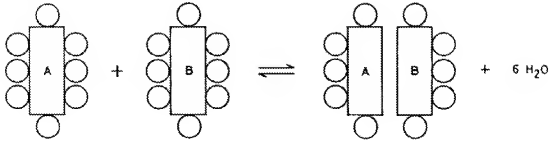


Fig. 2-6. The formation of a hydrophobic interaction between two hydrocarbon molecules A and B (the circles represent water molecules) [78].

in water is exothermic ($\Delta H < 0$) it follows from $\Delta G = \Delta H - T \cdot \Delta S$ that the entropy of the system must decrease. This can be interpreted as a consequence of the highly ordered structure of the water molecules around the dissolved hydrocarbon molecules. In other words, the water molecules are more tightly packed around the dissolved hydrocarbon molecules than in pure water. This is called a structure increase. If aqueous solutions of two hydrocarbons are mixed, the two hydrocarbons may form an aggregate with simultaneous partial reconstruction of the original undisturbed water structure. This is shown schematically in Fig. 2-6.

Due to the contact between A and B, fewer water molecules are now in direct contact with the hydrocarbon molecules. Thus, the ordering influence of the hydrophobic molecules will be diminished and the entropy increases ($\Delta S > 0$). Although thermal energy is required for the destructuring of the hydration shells around A and B ($\Delta H > 0$), the free energy diminishes upon aggregation ($\Delta G < 0$). Therefore, it is energetically advantageous for apolar molecules, or apolar groups in otherwise polar molecules, when dissolved in water, to aggregate with expulsion of water molecules from their hydration shells. In order to minimise the unfavourable solute/water interactions, the apolar solute molecules (or apolar groups) will interact preferentially, thus reducing the number of their water contacts [176]. This effect has been called *hydrophobic interaction.**) The water molecules around an inert apolar solute have a higher coordination and are thus more ordered than in the bulk liquid, which is entropically unfavourable. The aggregation of apolar solutes as shown in Fig. 2-6 releases water molecules into the bulk water, which is entropically very favourable.

This hydrophobic interaction can be illustrated by considering the thermodynamic parameters for the dissolution of the archetypal apolar hydrocarbon methane in cyclohexane (an apolar, non-associated solvent) and in water (a polar, strongly self-associated solvent); Table 2-7 [225].

The unfavorable Gibbs energy ($\Delta G_s^c \gg 0$) for the dissolution of methane in water is the result of a strongly negative entropy of solution ($\Delta S_s^c \ll 0$), which prevails over

* Glass beads can be used as an illustration of hydrophobia interactions. Thus, glass beads covered with dichloro-dimethylsilane can be regarded as solid hydrocarbon particles. Only hydrophobic interactions are possible. In a structured solvent such as water or formamide, the beads cluster together. When the polarity of the solvent is decreased by addition of alcohols the clusters disintegrate [79].

Table 2-7. Thermodynamic parameters for dissolution of gaseous methane in cyclohexane and water at 25 °C [225].

Solvents	ΔG_S°/(kJ · mol^{-1})	ΔH_S°/(kJ · mol^{-1})	ΔS_S°/(J · mol^{-1} · K^{-1})
Water	25.5	−13.8	−132
Cyclohexane	14.2	−3.0	−58

the favorable enthalpic contribution ($\Delta H_S^\circ < 0$). The negative enthalpy and entropy of transfer of methane from cyclohexane to water can be interpreted in terms of an increased degree of water-water hydrogen bonding in the solvation shell surrounding the apolar solute molecule.

Generally, the introduction of apolar molecules (such as hydrocarbons or noble gases), or apolar residues in otherwise polar molecules (such as alkyl side chains in biopolymers) into water leads to a reduction of the degrees of freedom (spatial, orientational, dynamic) of the neighbouring water molecules. This effect is called the *hydrophobic effect* or *hydrophobic hydration* [176]. *Hydrophobic* means 'water-fearing'. It should be noted that the interaction between hydrophobic molecules and water molecules is actually attractive because of the dispersion interactions. However, the water/water interaction is much more attractive. Water molecules simply love themselves too much to let some other compounds get in the way [26b]! Therefore, from the point of view of the water molecules, the term "hydrophobic" is rather a misnomer; it would be better to refer to water as being "lipophobic".

This hydrophobic hydration was first postulated by Frank and Evans in 1945. They wrote: "The nature of deviation found for non-polar solutes in water leads to the idea that the water forms frozen patches or microscopic icebergs around such solute molecules. The word 'iceberg' represents a microscopic region, surrounding the solute molecule, in which water molecules are tied together in some sort of quasi-solid structure" [226].

The model of "icebergs" around nonpolar solute molecules in aqueous solution is clearly not a very realistic one. However, if solutions of hydrocarbons (or noble gases) are cooled, then the solid phase that sometimes separates out consists of a so-called gas hydrate (clathrate), in which water provides a particular kind of hydrogen-bonded framework containing cages that are occupied by the nonpolar solute molecules. Obviously, such gas hydrates (clathrates) represent more realistic models for the phenomenon of hydrophobic hydration [176].

In principle, such interactions should also apply to other solvents resembling water, and therefore the more general term *solvophobic interactions* has been proposed [80, 343]. In fact, analogous water-like behaviour has been observed with self-associated solvents other than water, *e.g.* ethanol [81], glycerol [82], ethylammonium nitrate [227], and some dipolar non-HBD solvents [228].

Although there is overwhelming experimental evidence that the hydrophobic interaction is "entropy-driven", this classical view is still a matter of debate [79a, 167, 227, 229–231, 343–347]. For example, it has been claimed that the major contribution to the hydrophobic interaction between the methylene groups of *n*-alkanes is an enthalpic and not an entropic effect [230]. In other words, the poor solubility of non-

polar solutes in water should be due to unfavourable enthalpy and not to unfavourable entropy [227, 231].

Furthermore, what is the real origin of hydrophobicity (or solvophobicity), that is, which molecular property of water is primarily responsible for the positive Gibbs energy of hydration of nonpolar solutes and their tendency to associate? The two main physical explanations are:

(a) the high cohesive pressure of water (see Table 3-2 in Section 3.2), caused by the strong hydrogen-bonding interactions compared to the weak interactions between water and nonpolar solutes; and/or
(b) the small size of the water molecules, which increases the entropic cost of opening up a cavity to accommodate the solute. Opening up a cavity for solute molecules is entropically unfavourable in any solvent. However, the small size of water molecules exacerbates this situation and gives rise to entropies more negative that in other solvents with larger molecule size.

For a more detailed discussion of these questions, see references [76, 77, 176, 343–347] and references cited therein. More recent results [346, 347] have shown that the classical view (a) seems to be basically correct. The essential condition for solvophobicity is that solvent/solvent interactions are much stronger than solute/solvent interactions. However, the solvophobic effect is not necessarily always an entropic phenomenon; it can be enthalpic or entropic depending on the temperature and the geometrical size of the solute molecules [346].

Hydrophobic interactions are important in the aggregation of polymethine dyes [81] and in the stabilization of particular conformations of polypeptides and proteins in aqueous solution [222, 232]. They also play an important role in the biochemical complexation between an enzyme and a substrate [77, 78, 83, 84, 348].

Hydrophobicity parameters for organic substituents have been developed by Hansch *et al.* using partitioning phenomena [296], and by Menger *et al.* using kinetic measurements (hydrolysis of long-chain esters) [297]; see Section 7.2. Further results connected with the presence of hydrophobic interactions in solutions are discussed in Sections 2.5 and 5.4.8.

2.3 Solvation [49, 85–98, 98a, 233–241]

The term *solvation* refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules. This solvent shell is the result of intermolecular forces between solute and solvent. For aqueous solutions the term used is *hydration*. Intermolecular interactions between solvent molecules and ions are particularly important in solutions of electrolytes, since ions exert specially strong forces on solvent molecules. Crude electrostatic calculations show that the field experienced by nearest neighbours of dissolved ions is $10^6 \ldots 10^7$ V/cm. Fig. 2-7 shows a highly simplified picture of such an interaction between ions and dipolar solvent molecules.

The *solvation energy* is considered as the change in Gibbs energy when an ion or molecule is transferred from a vacuum (or the gas phase) into a solvent. The Gibbs

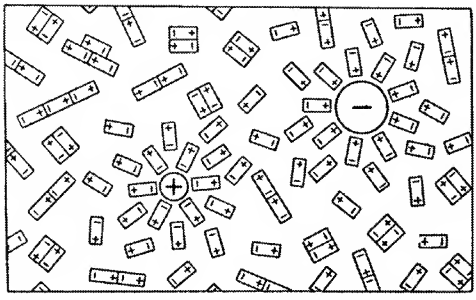


Fig. 2-7. Solvation of ions in a solvent consisting of dipolar molecules [99]. The charges of the dipolar molecules are in fact partial charges $\delta\oplus$ and $\delta\ominus$.

energy of solvation, ΔG°_{solv}, a measure of the solvation ability of a particular solvent, is the result of a superimposition of four principal components of a different nature [100]:

(a) the cavitation energy associated with the hole that the dissolved molecule or ion produces in the solvent;
(b) the orientation energy corresponding to the phenomenon of partial orientation of the dipolar solvent molecules caused by the presence of the solvated molecule or ion (*cf.* Fig. 2-7);
(c) the isotropic interaction energy corresponding to the unspecific intermolecular forces with a long radius of activity (*i.e.* electrostatic, polarisation, and dispersion energy);
(d) the anisotropic interaction energy resulting from the specific formation of hydrogen bonds or electron-pair donor/electron-pair acceptor bonds at well localized points in the dissolved molecules.

The dissolution of a substance requires that not only the interaction energy of the solute molecules (for crystals the lattice energy*) be overcome but also the interaction energy between the solvent molecules themselves. This is compensated by the gain in Gibbs energy of solvation, ΔG°_{solv}. The standard molar Gibbs energy of solvation, ΔG°_{solv}, can be formulated as the difference between the Gibbs energy of solution, ΔG°_{soln},

* The lattice energy is the work required to separate to infinity the elements of the lattice from their equilibrium position at 0 K. For ionic lattices of the alkali halides it is of the order 628 ... 837 kJ/mol (150 ... 200 kcal/mol) [49]. For molecular lattices of organic compounds such as benzene, naphthalene, and anthracene it is of the order 42 ... 105 kJ/mol (10 ... 25 kcal/mol) [101]. The experimental heat of sublimation of benzene is 44.6 kJ/mol (10.7 kcal/mol) [102].

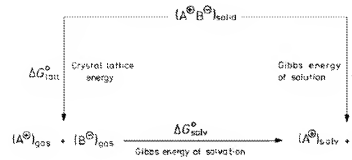


Fig. 2-8. The relationship between standard molar Gibbs energies of solvation and solution and the crystal lattice energy of an ionophore $A^{\oplus}B^{\ominus}$; $\Delta G^{\circ}_{solv} = \Delta G^{\circ}_{soln} - \Delta G^{\circ}_{latt}$.

and the crystal lattice energy, ΔG°_{latt}, as shown by means of the customary Born-Haber cycle in Fig. 2-8.

If the liberated solvation energy is higher than the lattice energy, then the overall process of dissolution is exothermic. In the opposite case the system uses energy and the dissolution is endothermic. The values for NaCl are typical: lattice energy +766 kJ/mol, hydration energy −761 kJ/mol, and energy of solution +3.8 kJ/mol. The energies of solution are generally small because interaction within the crystal lattice is energetically similar to interaction with the solvent.

The Gibbs energies of solvation of individual ions cannot be directly measured but they can be calculated [49]. The Gibbs energies of hydration of some representative ions are collected in Table 2-8. It can be seen that these values can be as high as bond energies or even higher (209 ... 628 kJ/mol; 50 ... 150 kcal/mol). Consequently, the solvent is often considered a direct reaction partner and should really be included in the reaction equation. The isolation of numerous solvates such as hydrates, alcoholates, etherates, and ammoniates, especially of inorganic or organometallic compounds, are examples. Between the two extremes, *viz.* the simple solvation resulting from weak

Table 2-8. Standard molar Gibbs energies of hydration, ΔG°_{hydr}, of some representative single ions at 25 °C [241, 242][a].

Cations	ΔG°_{hydr}/(kJ · mol^{-1})	Anions	ΔG°_{hydr}/(kJ · mol^{-1})
$H^{\oplus}$	−1056	$F^{\ominus}$	−472
$Li^{\oplus}$	−481	$Cl^{\ominus}$	−347
$Na^{\oplus}$	−375	$Br^{\ominus}$	−321
$K^{\oplus}$	−304	$I^{\ominus}$	−283
$Mg^{\oplus\oplus}$	−1838	$HO^{\ominus}$	−439
$Al^{\oplus\oplus\oplus}$	−4531	$SO_4^{\ominus\ominus}$	−1090

[a] For a comprehensive compilation of Gibbs energies of solvation, see C. M. Criss and M. Salomon: *Thermodynamic Measurements — Interpretation of Thermodynamic Data.* In A. K. Covington and T. Dickinson (eds.): *Physical Chemistry of Organic Solvent Systems*, Plenum Press, London & New York 1973, p. 253 ff. — *Cf.* also D. W. Smith: *Ionic Hydration Enthalpies*, J. Chem. Educ. *54*, 540 (1977). — A critical selection of standard molar heat capacities of hydration, $\Delta_{hyd}C^{\circ}_{p}$/(J · K^{-1} · mol^{-1}), of single ions has been given by M. H. Abraham and Y. Marcus, J. Chem. Soc., Faraday Trans. I *82*, 3255 (1986).

intermolecular interactions, and the *bona fide* chemical modification of the substrate by the solvent, all other possibilities exist.

The most direct measure of the energetics of ion solvation is, without doubt, their *standard molar Gibbs energy of solvation, i.e.* transfer from the gas phase to the solvent (*cf.* Fig. 2-8). However, this quantity is generally unknown, particularly for ions in nonaqueous solvents. Therefore, ΔG°_{solv} is advantageously replaced by the *standard molar Gibbs energy of transfer* of the ion X from water, W, as reference solvent, to another solvent, S, $\Delta G^\circ_t(X, W \rightarrow S)$, as defined by Eq. (2-12a):

$$\Delta G^\circ_t(X, W \rightarrow S) = \mu^\circ_X(\text{in S}) - \mu^\circ_X(\text{in W}) = R \cdot T \cdot \ln {}^W y^S_X \tag{2-12a}$$

μ°_X is the standard (*i.e.* infinite dilution) chemical potential of X and ${}^W y^S_X$ the so-called *solvent-transfer activity coefficient* of X.

In order to obtain the $\Delta G^\circ_t(X, W \rightarrow S)$ of individual ions from experimental data on complete electrolytes, the extrathermodynamic assumption that $\Delta G^\circ_t(Ph_4As^\oplus, W \rightarrow S) = \Delta G^\circ_t(Ph_4B^\ominus, W \rightarrow S)$ for all solvents has been made, using $Ph_4As^\oplus Ph_4B^\ominus$ as reference electrolyte ($Ph = C_6H_5$). This seems reasonable because the large symmetrical ions of tetraphenylarsonium tetraphenylborate are of comparable size, structure, and charge, and are, therefore, similarly solvated on transfer from one solvent to another. Arguments in favour of and against this extrathermodynamic assumption have been reviewed [235, 241, 243, 244]*).

Experimentally, the molar Gibbs energy of transfer of an anion $X^\ominus$ is obtained from the combined results of four solubility measurements, namely of the salts $Ph_4As^\oplus Ph_4B^\ominus$ and $Ph_4As^\oplus X^\ominus$ in water, W, and of the same salts in the solvent S. The Gibbs energy of transfer is then:

$$\Delta G^\circ_t(X^\ominus, W \rightarrow S) = R \cdot T[2 \cdot \ln s(Ph_4AsX, W) - 2 \cdot \ln s(Ph_4AsX, S) + \ln s(Ph_4AsPh_4B, S) - \ln s(Ph_4AsPh_4B, W)] \tag{2-12b}$$

where s is the solubility, expressed on the molar scale ($mol \cdot l^{-1}$).

Table 2-9 collects selected values of $\Delta G^\circ_t(X, W \rightarrow S)$ obtained on this basis, taken from the extensive and critically evaluated compilations of Marcus [244, 349] and Gritzner [350]. A nice graphical representation of the changes in ΔG°_t, ΔH°_t, and ΔS°_t for

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* Analogously, the following extrathermodynamic "reference electrolyte" assumptions are widely used:

$$\Delta H^\circ_t(Ph_4As^\oplus, W \rightarrow S) = \Delta H^\circ_t(Ph_4B^\ominus, W \rightarrow S),$$

and similarly

$$\Delta S^\circ_t(Ph_4As^\oplus, W \rightarrow S) = \Delta S^\circ_t(Ph_4B^\ominus, W \rightarrow S),$$

for the transfer from water to all solvents at any temperature [244]. This is equivalent to assuming that the molar Gibbs energy of transfer, $\Delta G^\circ_t(X, W \rightarrow S)$, at a given reference temperature (usually 298.15 K) is valid for all temperatures [244].

Table 2-9. Selected standard molar Gibbs energies of transfer of single ions X from water (W) to seven nonaqueous solvents (S), $\Delta G_t^\circ(X, W \rightarrow S)$/(kJ · mol^{-1})[a], at 25 °C (molar scale), taken from the compilation of Marcus [244]. Values for $F^\oplus$ were taken from G. T. Hefter, Pure Appl. Chem. 63, 1749 (1991).

X	S						
	CH_3OH	C_2H_5OH	CH_3COCH_3	$HCON(CH_3)_2$	CH_3CN	CH_3SOCH_3	$[(CH_3)_2N]_3PO$
$H^\oplus$	10.4	11.1		−18	46.4	−19.4	
$Li^\oplus$	4.4	11		−10	25	−15	
$Na^\oplus$	8.2	14		−9.6	15.1	−13.4	
$K^\oplus$	9.6	16.4	4	−10.3	8.1	−13.0	−16
$Ag^\oplus$	6.6	4.9	9	−20.8	−23.2	−34.8	−44
$(CH_3)_4N^\oplus$	6	10.9	3	−5.3	3	−2	
$(C_6H_5)_4As^\oplus$[b]	−24.1	−21.2	−32	−38.5	−32.8	−37.4	−39
$F^\ominus$	16	26	79	85	71	73	
$Cl^\ominus$	13.2	20.2	57	48.3	42.1	40.3	58
$Br^\ominus$	11.1	18.2	42	36.2	31.3	27.4	46
$I^\ominus$	7.3	12.9	25	20.4	16.8	10.4	30
$CN^\ominus$	8.6	7	48	40	35	35	
$ClO_4^\ominus$	6.1	10		4	2		−7
$(C_6H_5)_4B^\ominus$[b]	−24.1	−21.2	−32	−38.5	−32.8	−37.4	−39

[a] A positive value of $\Delta G_t^\circ(X, W \rightarrow S)$ means that the ion is better solvated by water than by solvent S; a negative value means that the ion is more strongly solvated after transfer from water to solvent S.

[b] See text for the so-called tetraphenylarsonium tetraphenylborate assumption.

the transfer of univalent single ions from water to other solvents has been given by Persson [301]. See Section 5.5.3 for further discussions.

The following three aspects are also of importance in solvation: the stoichiometry of the solvate complexes (normally described by the coordination or solvation number), the lability of the solvate complexes (usually described by the rate of exchange of the molecules of the solvent shell with those of the bulk solvent), as well as the fine structure of the solvation shell (for water often described by the simple model of ion solvation of Frank and Wen [16]).

Coordination and solvation numbers reflect the simple idea that the solvation of ions or molecules consists of a coordination of solute and solvent molecules. The *coordination number* is defined as the number of solvent molecules in the first coordination sphere of an ion in solution [103]. This first coordination sphere is composed only of solvent molecules in contact with or in bonding distance of the ion such that no other solvent molecules are interposed between them and the ion. This kind of solvation is sometimes termed *primary* or *chemical solvation*. Coordination numbers, determined by different experimental techniques [103], range in water from approx. 4 for $Be^{2\oplus}$ to approx. 9 for $Th^{4\oplus}$, although the majority of the values are close to 6 (*e.g.* for $Al^{3\oplus}$).

The *solvation number* is defined as the number of solvent molecules per ion which remain attached to a given ion long enough to experience its translational movements [94, 97, 104]. The solvation number depends upon the reference ion and its assumed solvation number as well as upon the method of measurement. Depending on the method of measurement, solvent molecules loosely bound in the second or in a higher sphere may be included. The partial ordering of more distant solvent molecules beyond the primary solvation shell is termed *secondary* or *physical solvation*. For example, mobility measurements indicate the number of solvent molecules moving with the ion, while dielectric measurements indicate only the number of solvent molecules in the first sphere. The solvation number of $Li^{\oplus}$ in water, determined using different electrolytic transference methods, varies therefore between 5 and 23. An inspection of the solvation numbers measured by electrolytic transport methods shows that the order of hydration numbers of the alkali metal cations is: $Li^{\oplus} > Na^{\oplus} > K^{\oplus} > Rb^{\oplus} > Cs^{\oplus}$. The alkaline earth metal cations are more highly solvated than the alkali cations ($Mg^{\oplus\oplus} > Ca^{\oplus\oplus} > Sr^{\oplus\oplus} > Ba^{\oplus\oplus}$). The more dilute the solution the greater the solvation of a given ion. The halogen anions are hydrated in the order $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$. Therefore, as a rule it can be stated that the smaller the ion and the greater its charge, the more highly it is solvated [94, 97, 104]. Conductance data show, that the solvation number for a given ion varies strongly with the solvent. Thus, the solvation number of $Li^{\oplus}$ varies from 1.4 in sulfolane, 7 in methanol, 9 in acetonitrile to 21 in water. The conductance data also indicate that in all organic solvents used, the solvation of the alkali metal cations is in the order: $Li^{\oplus} > Na^{\oplus} > K^{\oplus} > Rb^{\oplus} > Cs^{\oplus}$. The order of solvation of the halogen anions in the organic solvents studied is, in general, $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ [94, 97, 104].

Even in the case of strong interactions between solvent and solute, the life time of each solvate is brief since there is continuous rotation or exchange of the solvent shell molecules. The time required for reorientation of hydrates in water is of the order $10^{-10} \ldots 10^{-11}$ s at 25 °C [91]. If the exchange between bulk solvent molecules and those in the inner solvation shell of an ion is slower than the NMR time scale, then it is possible to observe two different resonance signals for the free and bound solvent. In this

way, it has been shown, using ^{17}O NMR spectroscopy, that the hexaaquo hydration spheres of $Al^{3\oplus}$ and $Cr^{3\oplus}$, and the four water molecules bound by $Be^{2\oplus}$ exchange at a rate of less than 10^4/s, while those of the alkali metal cations exchange at a rate faster than 10^4/s [96, 105].

In general, since solvent molecules directly bound to an ion have different chemical shifts from those of the bulk solvent, NMR spectroscopy is a very useful method for studying solvation shells [106–111]. If the exchange rates are too high, however, the NMR signals coalesce to a single time-averaged resonance signal. It is usually assumed that solvent molecules in environments other than the first coordination sphere are exchanging at diffusion-controlled rates and therefore appear in the environmentally averaged bulk solvent resonance. A variety of different solvent nuclei have been used for this purpose: ^1H, ^{13}C, ^{17}O, and ^{31}P. As an example, the ^1H NMR spectrum of 2.1 M aqueous solution of $Al(NO_3)_3$ at −40 °C shows two signals [112]. The low-field signal arises from the coordinated solvent, and the high-field resonance from the bulk solvent. Two ^{13}C NMR signals are also observed for aqueous dimethyl sulfoxide containing $AlCl_3$ at 30 °C, one for the bulk and one for the bound solvent (1.94 ppm upfield) [113].

The ^1H NMR spectrum of an aqueous $Al(ClO_4)_3$ solution in [D_6]acetone shows nicely the two different signals of bulk water and hydration water in the $Al^{3\oplus}$ inner shell, even at room temperature [245]. The addition of acetone slows down the proton exchange rate. A primary hydration number of six for $Al^{3\oplus}$ has been obtained in this way [245].

Another approach to the study of ion-solvent interactions involves the determination of the solvent effect on the resonance frequency of the solute ion, using nuclei of spin $I \neq 0$ such as ^7Li, ^{23}Na, ^{27}Al, ^{35}Cl, ^{59}Co, ^{69}Ga, ^{133}Cs, ^{195}Pt, and ^{205}Tl [106–111, 111a, 246, 247, 294]. $^{205}Tl^{\oplus}$ is an exceptionally sensitive ion [294]. In going from water to pyridine the change in resonance frequency is approximately 782 ppm (!) [114]. In comparison, the change in chemical shift for $^{23}Na^{\oplus}$ in these two solvents is only about 1.3 ppm [115]. Therefore, $^{205}Tl^{\oplus}$ and other ions are very useful probes for the study of solvation and solvent structure. The greater the Lewis basicity of the solvent, the higher the resonance frequency of the $^{205}Tl^{\oplus}$ ion. The increase in resonance frequency with increasing solvent Lewis basicity can be considered as a measure of the strength of interaction between the solute ion and solvent molecules [294].

Other spectroscopic methods have also been used to study the statics and dynamics of solvation shells of ions and molecules [351–354]. In this respect, *solvation dynamics* refers to the solvent reorganization (*e.g.* rotation, reorientation, and residence time of solvent molecules in the first solvation shell) in response to an abrupt change in the solute properties, *e.g.* by photoexcitation of the solute with ultra-short laser-light pulses. Provided that this excitation is accompanied by an electron transfer or a change in the dipole moment, then the dynamics of this process correspond to how quickly the solvent molecules rearrange around the instantaneously created charge or the new dipole.

A number of models have been developed to describe the fine structure of the solvent shells of ions and molecules. While the agreement with experimental findings is more or less satisfactory, it is for the most part only qualitative (for reviews, see references [85, 91, 94, 95, 98]). According to the influence of the solute on the solvent structure, two different types of solvent can be distinguished (Fig. 2-9) [98]. In the former case, the pure solvent does not show a high degree of order. The directional properties of

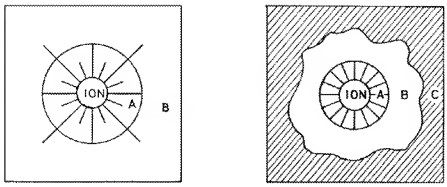


Fig. 2-9. Schematic multizone models for ion solvation in solvents: (a) with low degree of order such as hydrocarbons, consisting of solvation shell A and disordered bulk solvent B [98]; (b) in highly ordered solvents such as water, consisting of solvation shell A with immobilized solvent molecules, followed by a structure-broken region B, and the ordered bulk solvent C (Frank and Wen [16]).

the dissolved ion dominate in a rather large region around the center and decrease gradually on proceeding into the unperturbed bulk solvent. The solution consists of an ordered sphere – the primary solvation shell A – and the disordered bulk solvent B (Fig. 2-9a) [98].

In the latter case, the solvent possesses a highly ordered structure such as that found in water. Frank and Wen [16] distinguish between three different regions in the solvent surrounding a solute. In the first coordination sphere A, the solvent molecules are strongly bound to the ion and therefore appear less mobile than the molecules in the bulk solvent. At some distance from the ion there exists the normal structure of the pure ordered solvent C. Between A and C, according to Frank and Wen [16], lies an intermediate region of disorder B, with highly mobile solvent molecules. This has been introduced in order to explain the "structure making" and "structure breaking" properties of ions of different charge and size in aqueous solutions. The concept of different regions around the dissolved ion was developed by Gurney [116], who introduced the term *cosphere* for the zone surrounding a spherical ion in which significant differences in structure and properties of solvent molecules are to be expected*). In contrast to the ordinary strong *positive hydration* of small spherical ions possessing a structure-making effect on the solvent molecules (*cf.* Fig. 2-9a), water molecules around a dissolved ion are in some cases more mobile than in pure water. In other words, the exchange frequency of water molecules around the ions is greater than in regions of pure water (*cf.* region B in Fig. 2-9b). This explains the experimental observation that aqueous solutions of certain salts such as potassium iodide show a greater fluidity than pure water at the same temperature. This effect has been called *negative hydration* [85] and it is con-

* In a liquid, the formation of temporary solvent molecule groups which have some crystalline character has been called *cybotaxis* (Greek, κυβεύω, dice-play, τάξις, an arrangement) by Stewart [116a]; see also [116b]. A *cybotactic region* may then be defined as the volume around a solute molecule in which the ordering of the solvent molecules has been influenced by the solute, including both the first solvation shell and the transition region; *cf.* [129].

nected with the structure-breaking effect of large singly-charged spherical ions on solvent molecules [91, 117]. The structure-breaking effect of large ions is not restricted to water as a solvent. Ethylene glycol and glycerol are liquids which also show this effect for a number of salts that cause structure-breaking in water [117]. To date, however, the validity of the multizone models for ion solvation proposed by Frank and Wen [16] and others has lacked direct experimental proof [117]. Consequently, owing to the lack of detailed knowledge of the solvents' structure and of satisfactory molecular theories for associated liquids, all attempts at a detailed description of solvation shells are still imperfect.

The solubility of a dissolved non-electrolyte solute can be reduced by the addition of a salt. This phenomenon, known as the *salting-out effect*, is of practical importance for the isolation of organic compounds from their solutions. In the presence of a dissolved dissociated salt, a fraction of the solvent molecules becomes involved in solvational interaction with the ions of the electrolyte, whereby their activity is diminished, leading to salting-out of the dissolved non-electrolyte solute. In other words, the salting-out can be considered as the difference in solubility in two kinds of solvents, the ion-free and the ion-containing one [248].

Theoretical chemists have developed a variety of methods and computational strategies for describing and understanding the complex phenomenon of solvation [27d, 355–358]. Altogether, three general approaches have been used for the theoretical description of solute/solvent interactions:

(a) quantum-chemical continuum models, where the solvent is treated as a structureless, *i.e.* continuous and homogeneous, medium that surrounds the solute ions or molecules like a bath, characterized solely by its relative permittivity ε_r. The solvated species (ions, polar molecules) induce polarization charges in the surrounding solvent continuum that in turn give rise to an extra electric field in the vicinity of the solute, called (Onsager) reaction field [357, 359; and references cited therein];
(b) supramolecular models, which treat the solvent molecules around the solute on the same footing as the solute, *i.e.* as discrete particles in an ensemble of solute and solvent species, using Monte Carlo statistical mechanics or molecular dynamics techniques [360, 361; and references cited therein];
(c) semicontinuum quantum-chemical models, which retain the reaction field contribution, but the direct electrostatic solute/solvent interactions in the first solvation shell are modeled differently. That is, the supermolecule (solute + first solvation shell) is surrounded by a continuum solvent [362–364; and references cited therein].

Particularly during the last decade, much progress has been made in the theoretical description of solvation. However, when applied to actual solutes, all models still have their limitations and flaws. For comprehensive reviews on theoretical treatments of solvation phenomena, see references [27d, 355–358].

2.4 Selective Solvation [89, 94, 96, 118–120, 241, 249, 250]

The description of solvation of ions and molecules in solvent mixtures is even more complicated. Besides the interaction between solvent and solute, the interaction between unlike solvent molecules plays an important supplementary role. This leads to large

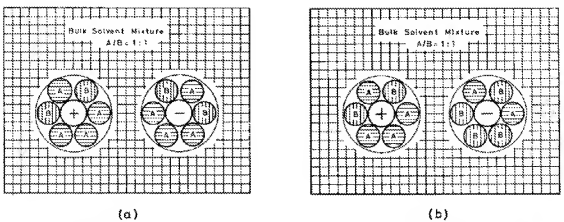


Fig. 2-10. Schematic model for the selective solvation of ions by one component of a binary 1:1 mixture of the solvents A and B [119].
(a) Homoselective solvation: both ions are preferentially solvated by the same solvent A.
(b) Heteroselective solvation: the cation is preferentially solvated by A and the anion by B.

deviations from the ideal behaviour expected from Raoult's law of vapour pressure depression of binary mixtures; see references [365, 366] for reviews on the physicochemical properties of solvent mixtures. Typical examples of the non-ideal behaviour of binary solvent mixtures are water/alcohol [19], dimethyl sulfoxide/methanol [367], as well as water/methanol and water/acetonitrile mixtures [368]. When water is mixed with methanol an exothermic mixing enthalpy is observed, whereas in the case of acetonitrile the enthalpy of mixing is endothermic [368].

From investigations of the solvation of ions and dipolar molecules in binary solvent mixtures it has been found that the ratio of the solvent components in the solvent shell can be different from that in the bulk solution. As expected, the solute is surrounded preferably by the component of the mixture which leads to the more negative Gibbs energy of solvation, ΔG°_{solv}. The observation that the solvent shell has a composition other than the macroscopic ratio is termed *selective* or *preferential solvation* (*cf.* Fig. 2-10). These terms are generally used to describe the molecular-microscopic local solute-induced inhomogeneity in a multicomponent solvent mixture. They include both (i) nonspecific solute/solvent association caused by dielectric enrichment in the solvent shell of solute ions or dipolar solute molecules, and (ii) specific solute/solvent association such as hydrogen-bonding or EPD/EPA interactions.

When in a mixture of two solvents, both ions of a binary salt are solvated preferably by the same solvent, the term applied is *homoselective solvation* (Fig. 2-10a). Similarly, the preferred solvation of the cation by one, and the anion by the other solvent, is termed *heteroselective solvation* (Fig. 2-10b) [119]. Thus, in a solution of silver nitrate in the binary solvent mixture acetonitrile/water, a preferential solvation of $Ag^{\oplus}$ by acetonitrile and of $NO_3^{\ominus}$ by water was observed (heteroselective solvation) [121, 369][*]. In contrast, in solutions of calcium chloride in water/methanol mixtures, both $Ca^{2\oplus}$ and $Cl^{\ominus}$ are solvated largely by water (homoselective solvation) [122]. $Zn^{2\oplus}$ (from $ZnCl_2$) in

[*] The reasons for preferential solvation of $Ag^{\oplus}$ ions by acetonitrile in acetonitrile/water mixtures and the solvation shell structure of silver ions have been discussed [251].

the solvent mixture water/hydrazine is preferentially solvated by hydrazine; in an acetonitrile/water mixture solvation is largely by water [123]. Ag_2SO_4 is heteroselectively solvated in methanol/dimethyl sulfoxide mixtures: the silver ion is preferentially solvated by dimethyl sulfoxide, whereas the sulfate ion is preferably solvated by methanol. The Ag_2SO_4 salt is only sparingly soluble in methanol and in dimethyl sulfoxide. Its solubility is higher in mixtures of the two solvents than in the neat liquids, since both the cation and the anion can be solvated with the solvent component for which it has a greater affinity [123a]. A study of silver(I) salts in the *isodielectric* mixture of methanol ($\varepsilon_r = 32.7$) and *N*-methylpyrrolidin-2-one (NMP; $\varepsilon_r = 32.2$) showed heteroselective solvation of Ag^+ by NMP and the anions (SO_4^{2-}, BrO_3^-, IO_3^-) by methanol [370]. The $Cu^{\oplus}$ ion (from $CuClO_4$) shows strong preferential solvation by acetonitrile in acetonitrile/acetone mixtures, which may be of interest in the hydrometallurgical purification of copper [252]. Even protons exhibit preferential solvation by amines in mixed water/amine ion clusters studied in the gas phase [253].*)

In a binary mixture of solvents S_1 and S_2, a cation $M^{z\oplus}$ with a coordination number k and charge $z^{\oplus}$ forms $(k+1)$ cations of the type $[M(S_1)_i(S_2)_{k-i}]^{z\oplus}$ with $i = 0 \ldots k$, differently solvated in the first solvation shell. These differently solvated species have been called *solvatomers* [254]. For example, with octahedrally coordinated cations ($k = 6$), $k + 1 + 3 = 10$ solvatomers are to be expected (including three *cis/trans* isomeric solvatomers with $i = 2$, 3, or 4). In favourable cases, the concentrations of all solvatomers have been obtained as a function of the solvent mole fraction by NMR measurements [254].

Preferential solvation is not restricted to ions of electrolytes dissolved in multicomponent solvent systems. Even for dipolar nonelectrolyte solutes the composition of the solvation shell can deviate from that of the bulk solvent mixture, as shown for β-disulfones [255] and *N*-methylthiourea [256].

Different methods for the study of selective solvation have been developed [118, 120]: conductance and Hittorf transference measurements [119], NMR measurements (especially the effect of solvent composition on the chemical shift of a nucleus in the solute) [106–109], and optical spectra measurements like IR absorption shifts [111] or UV/Vis absorption shifts of solvatochromic dyes in binary solvent mixtures [124, 249, 371]. Recently, the preferential solvation of ionic (tetralkylammonium salts) and neutral solutes (phenol, nitroanilines) has been studied particularly successfully by ^1H NMR spectroscopy through the analysis of the relative intensities of intermolecular ^1H NOESY cross-peaks [372].

A convenient measure of the degree of selective solvation is the bulk solvent composition at which both solvents of a binary mixture participate equally in the contact solvation shell. This is the solvent composition at which the NMR chemical shifts lie midway between the values for the two pure solvents. This composition has been called the *equisolvation* or *iso-solvation point* (usually expressed in mole fractions of one solvent) [125]. According to Fig. 2-10, this point describes the bulk solvent composition at which both solvents A and B participate equally in the solvation shell of the cation or the anion, respectively.

*) A comprehensive tabulation of selective solvation of ions in a number of binary solvent systems is given by Gordon [96] (p. 256).

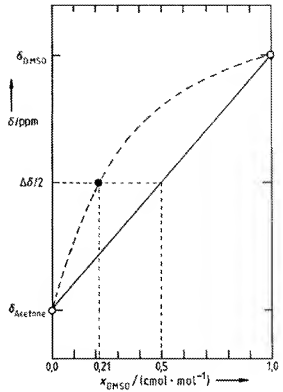
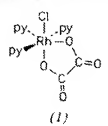


Fig. 2-11. NMR chemical shift of $^{23}Na^{\oplus}$ as a function of the mole fraction of dimethyl sulfoxide (DMSO) in a binary mixture of DMSO and acetone (according to [295]). *Straight line:* ideal case without preferential solvation, primary solvation shell of the same composition as the bulk solvent mixture. *Curved line:* real case with preferential solvation of $^{23}Na^{\oplus}$ by DMSO and iso-solvation point at $x_{DMSO}/(cmol \cdot mol^{-1}) \approx 0.21$, that is, the mole fraction of the bulk solvent for which the solvated ion chemical shift is the average of the shifts obtained in the pure solvents ($\Delta\delta = \delta_{DMSO} - \delta_{Acetone}$).

A useful probe of the immediate chemical environment of solute ions is the NMR chemical shift of alkali metal ions obtained in binary solvent mixtures [111, 126, 295]. These measurements are based on the assumption that the chemical shift of the solute cation is determined in an additive fashion by the solvent molecules comprising the first solvation shell. For example (*cf.* Fig. 2-11), the iso-solvation point of $^{23}Na^{\oplus}$ in dimethyl sulfoxide/acetone mixtures occurs at $x \approx 0.21$ cmol/mol dimethyl sulfoxide, indicating the higher solvating ability of this solvent relative to acetone. As shown schematically in Fig. 2-11, the preferential solvation of $^{23}Na^{\oplus}$ by dimethyl sulfoxide displaces its chemical shift towards δ_{DMSO} and a deviation from the straight line is observed.

The iso-solvation points obtained from $^{23}Na^{\oplus}$ chemical shifts of sodium tetraphenylborate in different binary solvent mixtures indicate the following relationships between the solvating abilities of pairs of organic solvents: $CH_3SOCH_3 \gg CH_3NO_2$; pyridine $> CH_3NO_2$; $CH_3SOCH_3 > CH_3CN$; pyridine $> CH_3CN$; $C_6H_5CN > CH_3NO_2$; $CH_3SOCH_3 >$ pyridine [126].

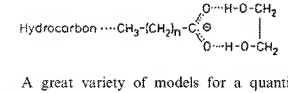
The term selective solvation also applies when one and the same dipolar molecule is preferentially solvated at two different loci by two different solvents. An example is the



(1)

chloro-oxalato-tripyridine-rhodium(III) complex (*I*), which dissolves in a 1:1 mixture of pyridine and water, but not in either pure water or pyridine [127]. Presumably, a Gibbs energy of solvation large enough to overcome the lattice forces is attained only by selective solvation of the three pyridine ligands by pyridine, and of the oxalato ligand by water.

Many macromolecular compounds dissolve in mixtures better than in pure solvents [20]. Thus, poly(vinyl chloride) is insoluble in acetone as well as in carbon disulfide, but soluble in a mixture of the two. The opposite situation is also known. Malononitrile and *N,N*-dimethylformamide both dissolve polyacrylonitrile but a mixture of the two does not [20]. Soaps dissolve neither in ethylene glycol nor in hydrocarbons at room temperature but are quite soluble in a mixture of the two. Here, ethylene glycol solvates the ionic end, and the hydrocarbon the apolar end of the fatty acid chain [128].



A great variety of models for a quantitative description of the composition dependence of the physicochemical properties of solutes dissolved in binary solvent mixtures have been developed [257–261, 373–378]. For example, using a rather simple two-step solvent-exchange model [374, 377], the behaviour of seventy binary solvent mixtures towards a solvatochromic betaine dye (structure see Fig. 6-2 in Section 6.2.1) can be quite precisely described, even for so-called *synergetic* solvent mixtures [377].

A binary solvent mixture exhibits *synergistic effects* on a physicochemical solute property P if for some mixtures this property P has a value higher or lower than either properties P_1 and P_2 corresponding to the neat solvents S_1 and S_2 [379]. For example, the empirically determined solvent polarity of binary mixtures of HBD and HBA solvents is often larger than the polarities of the two neat components. Clearly, the formation of hydrogen-bonded 1:1 complexes between HBD ad HBA solvent molecules leads to a new, more polar medium [124, 249, 377] (see Chapter 7 for a definition of the term *solvent polarity*).

The non-ideal behaviour of a wide selection of binary solvent mixtures has been studied experimentally mainly by means of suitable solvatochromic dyes, the UV/Vis absorptions of which are solvent-dependent (*cf.* Section 6.2.1); see references [380–385] for some more recent examples. Conversely, the largely non-ideal solute behaviour in binary solvent mixtures has been used for the quantitative determination of the compositions of such solvent mixtures, *e.g.* for the determination of small water contents in organic solvents [386–388].

2.5 Micellar Solvation (Solubilization) [96, 128, 130–132, 220, 262–267]

Special conditions are found in solutions of large cations and anions possessing a long unbranched hydrocarbon chain, *e.g.* $CH_3{-}(CH_2)_n{-}CO_2^{\ominus}M^{\oplus}$, $CH_3{-}(CH_2)_n{-}SO_3^{\ominus}M^{\oplus}$, or $CH_3{-}(CH_2)_n{-}N(CH_3)_3^{\oplus}X^{\ominus}$ (with $n > 7$). Such compounds are known as *amphiphiles*, reflecting the presence of distinct polar and nonpolar regions in the

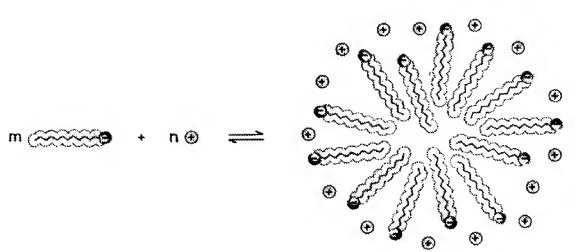


Fig. 2-12. Schematic two-dimensional representation of spherical micelle formation by an anionic amphiphile such as $CH_3{-}(CH_2)_{11}{-}CO_2^{\ominus}M^{\oplus}$ in water. The head group (⊖), the counterions (⊕), and the hydrocarbon chains are only schematically indicated to denote their relative position. The highly charged interface (ionic head groups plus bound counterions) between the micelle's hydrophobic core and the bulk solution is called the *Stern layer*. For a more realistic three-dimensional picture of a micelle, see references [264, 389].

molecule. Salts of such large organic ions are often highly aggregated in dilute aqueous solution. The resulting structured aggregates, together with counterions localized near their periphery by coulomb forces, are termed *micelles**). Fig. 2-12 gives a schematic representation of the formation of a spherical micelle by an anionic amphiphile.

The hydrophobic part of the aggregate molecules forms the core of the micelle while the polar head groups are located at the micelle-water interface in contact with the water molecules. Such micelles usually have average radii of 2...4 nm and contain 50...100 monomers in water. Their geometric structure is usually roughly spherical or ellipsoidal. In non-aqueous nonpolar solvents, the micellar structures are generally the inverse of those formed in water. In these solvents, the polar head groups form the interior of the micelle while the hydrocarbon chains of the ions are in contact with the nonpolar solvent.

At very low concentrations, ionic amphiphiles behave as normal strong electrolytes, but if the concentration is raised above the so-called critical *micelle* concentration (*cmc*; usually $10^{-4}...10^{-2}$ mol · l^{-1}), spherical aggregates are formed. Increasing the amphiphile (surfactant) concentration results in two different effects [264, 389]: (a) the increasing amphiphile concentration leads to an increased ionic strength of the aqueous bulk solution, thus decreasing the electrostatic repulsion between the head groups due to screening of their negative or positive charges; (b) for the hydrophobic hydrocarbon tails, an increase in the amphiphile concentration is unfavourable because of the increasing hydrophobic amphiphile/water interactions (see Section 2.2.7). Eventually,

* The term *micelle* was introduced in 1877 by Nägeli (from the Latin *mica*, a crumb) for a molecular organic aggregate of limited size without exact stoichiometry [270]. The existence of surfactant aggregates in aqueous soap solutions was established in 1896 by Krafft [271], and the first description of a surfactant micelle was given in 1913 by Reychler [272].

Table 2-10. Some typical surfactants (*surface active agents*) with their critical micelle concentrations (*cmc*) and aggregation numbers in aqueous solutions at 25 °C [268].

Surfactants	*cmc*/{mol · l^{-1}}	Aggregation number
Anionic		
Sodium 1-dodecyl sulfate (SDS)	0.0081	62
$CH_3{\cdots}(CH_2)_{11}{\cdots}OSO_3^{\ominus}Na^{\oplus}$		
Cationic		
1-Hexadecyl (= Cetyl)-trimethylammonium bromide (CTAB)	0.0013	78
$CH_3{\cdots}(CH_2)_{15}{\cdots}\overset{\oplus}{N}(CH_3)_3Br^{\ominus}$		
Nonionic		
Hexa(oxyethylene)dodecanol	0.00009	400
$CH_3{\cdots}(CH_2)_{11}{\cdots}(OCH_2CH_2)_6{\cdots}OH$		
Zwitterionic		
3-(*N*-1-Dodecyl-*N*,*N*-dimethylammonio)propane-1-sulfonate (SB 12)	0.003	55
$CH_3{\cdots}(CH_2)_{11}{\cdots}\overset{\oplus}{N}(CH_3)_2{\cdots}(CH_2)_3{\cdots}SO_3^{\ominus}$		

the driving force for dissolution of the amphiphile will be completely balanced by the forces working against the dissolution of the hydrophobic tails. Now, two different scenarios are possible: either a macroscopic phase separation will occur (*i.e.* formation of aggregates of infinite size), or micelles will be formed (*i.e.* formation of aggregates of finite size). Such micelles are thermodynamically stable, microheterogeneous, supramolecular species, dissolved in the aqueous bulk. They are characterized by the aforementioned *cmc* and the *micellar aggregation number*, both of which are dependent on the hydrocarbon tail length, the nature of the counter ion, and the ionic strength of the bulk solution.

Typical surfactants are listed in Table 2-10 along with their respective *cmc* values and aggregation numbers [268].

In reality, micellar systems are more complex than is implied by the simple static picture given in Fig. 2-12 (also known as the Hartley model [390]). A more realistic picture of micellar structures has been given by Menger [269]. According to his "porous cluster" or "reef" model, micelles possess rugged, dynamic surfaces, water-filled pockets, nonradial distribution of chains, and random distribution of terminal methyl groups. In fact, a micelle is a highly disorganized structure with multiple bent hydrocarbon chains, cavities, and even hydrocarbon/water contacts, and shows deviations from a precise spherical shape. A micelle is a dynamic molecular assembly which exists in equilibrium with its monomer, where monomer units are both leaving and entering the micelle. A monomer remains in a micelle for only $10^{-8} \ldots 10^{-3}$ s depending on the chain length of the surfactant molecule. Another, so-called surfactant-block model of micelles, has been given by Fromherz [273].

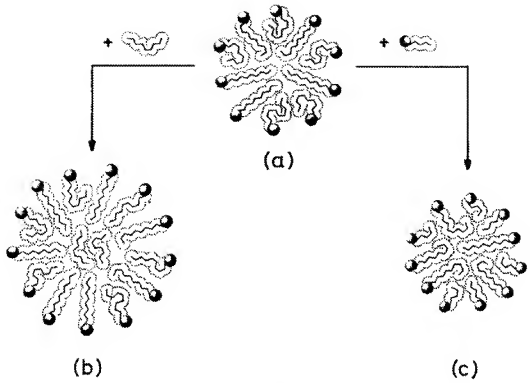


Fig. 2-13. Schematic two-dimensional representation of the solubilization of (b) *n*-nonane as a nonpolar substrate, and (c) 1-pentanol as another amphiphile, by a spherical ionic micelle (a) of an *n*-decanoic acid salt in water.

The existence of micelles in solutions of large ions with hydrocarbon chains is responsible for the observation that certain substances, normally insoluble or only slightly soluble in a given solvent, dissolve very well on addition of a surfactant (detergent or tenside). This phenomenon is called *solubilization* and implies the formation of a thermodynamically stable isotropic solution of a normally slightly soluble substrate (the *solubilizate*) on the addition of a surfactant (the *solubilizer*) [128, 133]. Non-ionic, nonpolar solubilizates such as hydrocarbons can be trapped in the hydrocarbon core of the micelle. Other amphiphilic solutes are incorporated alongside the principal amphiphile and oriented radially, and small ionic species can be adsorbed on the surface of the micelle. Two modes of solubilizate incorporation are illustrated in Fig. 2-13.

Because the micellar interior is far from being rigid, a solubilized substrate is relatively mobile. Like micelle formation, solubilization is a dynamic equilibrium process. Representative recent examples are the solubilization of benzene, naphthalene, anthracene, and pyrene in aqueous solution by the addition of 1-dodecanesulfonic acid [391], the solubilization of fullerene C_{60} in aqueous solutions of the non-ionic surfactant Triton X-100 [392], and the solubilization of a cholesteryl-group bearing pullulane (a hydrophobized polysaccharide) [393].

Essentially spherical micelles are not the only aggregates that can be formed in aqueous solution above the critical micelle concentration. Depending on the molecular structure of the amphiphile and the solution conditions (*e.g.* electrolyte concentration,

pH, temperature), inverted micelles, bilayers, vesicles, and biological membranes can readily be formed by spontaneous self-association [394] of certain amphiphilic molecules [130–132, 264]. In contrast to infinite *planar* bilayers, vesicles or liposomes (vesicles formed from lipids) are closed *spherical* bilayer aggregates that are much larger than micelles. Eventually, the mutual interaction of these aggregates at high concentrations (low water content) can lead to a transition to larger and more ordered *mesophases* or *lyotropic liquid crystalline* structures [264].

Not only solubilities, but also the rates and selectivities of organic reactions can be affected by the addition of surfactants to the reaction medium. The modification of chemical reactions by incorporating the reactant molecules into organized assemblies as a kind of microreactor has been the subject of considerable attention [274–277, 395, 396] (*cf.* also Section 5.4.8).

2.6 Ionization and Dissociation [49, 96, 134–139, 241, 278, 279]

Solutions of non-electrolytes contain neutral molecules or atoms*) and are non-conductors. Solutions of electrolytes are good conductors due to the presence of anions and cations. The study of electrolytic solutions has shown that electrolytes may be divided into two classes: *ionophores* and *ionogens* [134]. Ionophores (like alkali halides) are ionic in the crystalline state and they exist only as ions in the fused state as well as in dilute solutions. Ionogens (like hydrogen halides) are substances with molecular crystal lattices which form ions in solution only if a suitable reaction occurs with the solvent. Therefore, according to Eq. (2-13), a clear distinction must be made between the *ionization* step, which produces ion pairs by heterolysis of a covalent bond in ionogens, and the *dissociation* process, which produces free ions from associated ions [137, 397, 398].

$$\underset{\text{Ionogen}}{(A\text{-}B)_{solv}} \overset{K_{Ion}}{\rightleftharpoons} \underset{\text{Ion Pair}}{(A^{\oplus}B^{\ominus})_{solv}} \overset{K_{Dissoc}}{\underset{K_{Assoc}}{\rightleftharpoons}} \underset{\text{Free Ions}}{(A^{\oplus})_{solv} + (B^{\ominus})_{solv}} \tag{2-13}$$

$$K_{Ion} = [A^{\oplus}B^{\ominus}]/[A - B] \tag{2-14}$$

$$K_{Dissoc} = [A^{\oplus}] \cdot [B^{\ominus}]/[A^{\oplus}B^{\ominus}] \tag{2-15}$$

The index "solv" indicates that the species in parentheses are within one solvent cage.

Ionophores may exist in solution as an equilibrium mixture containing ion pairs and free ions. *Ion pairs* are defined as pairs of oppositely charged ions with a common solvation shell, whose life times are sufficiently long to render them recognizable kinetic entities in solution and for which only electrostatic binding forces are assumed [135]. Experimentally, ion pairs behave as one unit in determining electric conductivity, kinetic behaviour, and some thermodynamic properties (*e.g.* activity coefficient; osmotic pres-

*) An example of a monoatomic un-ionized substrate solution is that of mercury in air-free water, which contains zero-valent mercury atoms [140].

sure) of electrolyte solutions. In an external electric field such paired ions do not move individually but reorient themselves as an electric dipole. The ion-pair concept was introduced in 1926 by Bjerrum [280] to account for the behaviour of ionophores in solvents of low relative permittivity.

It is possible to distinguish between free ions from associated and covalently bonded species by conductivity measurements, because only free ions are responsible for electrical conductivity in solution [136, 399]. Spectrophotometric measurements distinguish between free ions and ion pairs on the one hand, and covalent molecules on the other, because in a first approximation the spectroscopic properties of ions are independent of the degree of association with the counterion [141]. The experimental equilibrium constant K_{exp}, obtained from conductance data, may then be related to the ionization and dissociation constants by Eq. (2-16).

$$K_{exp} = \frac{[A^{\oplus}] \cdot [B^{\ominus}]}{[A - B] + [A^{\oplus}B^{\ominus}]} = \frac{K_{Ion} \cdot K_{Dissoc}}{1 + K_{Ion}} \tag{2-16}$$

When the extent of ionization is small, then $K_{exp} = K_{Ion} \cdot K_{Dissoc}$ ($K_{Ion} \ll 1$ or $[A^{\oplus}B^{\ominus}] \approx 0$). For strong electrolytes, where $K_{Ion} \gg 1$, Eq. (2-16) reduces to $K_{exp} = K_{Dissoc}$.

Another equation, more comprehensive than Eq. (2-16), has been developed by Izmailov according to $K_{exp} = K_{dissoc}/(1 + K_{ion} + K^*)$, where K^* describes the equilibrium A—B + solv $\rightleftarrows$ $(A—B)_{solv}$ [412].

The two steps of Eq. (2-13), ionization and dissociation, are influenced in different ways by solvents. The coulombic force of attraction between two oppositely charged ions is inversely proportional to the relative permittivity of the solvent, according to Eq. (2-17). Therefore, only solvents with sufficiently high relative permittivities will be capable

$$U_{ion\text{-}ion} = -\frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z^{\oplus} \cdot z^{\ominus} \cdot e^2}{\varepsilon_r \cdot r} \tag{2-17}$$

(U = potential energy of an ion-ion interaction; $z \cdot e$ = charge on the ion; r = distance between the ions; ε_0, ε_r = permittivity of the vacuum and of the medium, resp.)

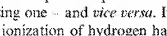
of reducing the strong electrostatic attraction between oppositely charged ions to such an extent that ion pairs can dissociate into free solvated ions. These solvents are usually called *dissociating solvents**).

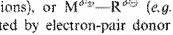
* Nernst [141a] and Thomson [141b] first showed independently that solvents of high relative permittivity promote the dissociation of ionic solutes. The term "dissociating solvent" was first used by Beckmann [141c] in connection with his ebullioscopic determination of the molecular mass of dissolved substances. Later on the term "smenogenic solvent" was proposed by Fuoss for solvents of low relative permittivity which favor the formation of ion pairs. Conversely, "smenolytic solvents" are those whose relative permittivities are high enough to prevent ion association [134]. The latter two terms have, however, found little application.

According to Eq. (2-17), for two isolated ions such as Na^+ and Cl^- in contact in vacuum ($\varepsilon_r = 1$), with $r = 276$ pm as the sum of the two ionic radii, the electrostatic binding energy is -8.4×10^{-19} J [26b]. This binding energy is of the order $200 \cdot kT$ per ion pair in vacuum, as compared to the thermal energy $kT = 4.1 \times 10^{-21}$ J at 300 K. Only at ion separation $r > 56000$ pm will the Coulomb energy fall below kT, which means that electrostatic Coulomb interactions are very strong and of long range [26b]. At ca. 500 kJ/mol ($=8.4 \times 10^{-19} \times 6.0 \times 10^{23}$), this interionic binding energy is similar to the energies of covalent bonds (*i.e.* 200–600 kJ/mol). The electrostatic interaction between oppositely charged ions can only be overcome by liberation of the molar Gibbs energy of solvation, ΔG°_{solv}, in transferring the ion pair from the gas phase (vacuum) into a medium with $\varepsilon_r \gg 1$.

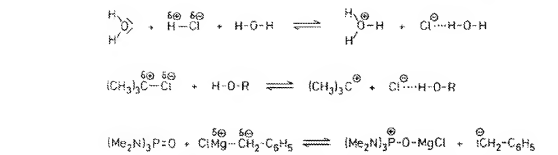
Ion association is only noticeable in aqueous solutions at very high concentrations because of the exceptionally high relative permittivity of water ($\varepsilon_r = 78.4$), but are found at much lower concentrations in alcohols, ketones, carboxylic acids, and ethers. In solvents of relative permittivities less than 10 ... 15, practically no free ions are found (*e.g.* in hydrocarbons, chloroform, 1,4-dioxane, acetic acid); on the other hand, when the relative permittivity exceeds 40, ion associates barely exist (*e.g.* water, formic acid, formamide). In solvents of intermediate relative permittivity ($\varepsilon_r = 15 \ldots 20$, *e.g.* ethanol, nitrobenzene, acetonitrile, acetone, *N*,*N*-dimethylformamide), the ratio between free and associated ions depends on the structure of the solvent as well as on the electrolyte (*e.g.* ion size, charge distribution, hydrogen-bonded ion pairs, specific ion solvation, *etc.*) [96]. Thus, lithium halides in acetone ($\varepsilon_r = 20.6$) are very weak electrolytes, whereas tetraalkylammonium halides are strongly dissociated in the same solvent [142–144]. In solvents of very low relative permittivity like benzene ($\varepsilon_r = 2.3$), very large association constants are usually found. This indicates that most ion pairs in such solutions exist in the form of higher aggregates [96].

The ability of a solvent to transform the covalent bond of an ionogen into an ionic bond, *i.e.* its *ionizing power*, is not determined in the first instance by its relative permittivity. Rather, the ionizing power of a solvent depends on its ability to function as an electron-pair acceptor or donor [53, 137]. A dissociating solvent is not necessarily an ionizing one – and *vice versa*. In most cases, ionization of bonds of the type $H^{\delta\oplus}—X^{\delta\ominus}$ (*e.g.* ionization of hydrogen halides), $R^{\delta\oplus}—X^{\delta\ominus}$ (*e.g.* ionization of haloalkanes in S_N1 reactions), or $M^{\delta\oplus}—R^{\delta\ominus}$ (*e.g.* ionization of organometallic compounds) is strongly assisted by electron-pair donor (EPD) and electron-pair acceptor (EPA) solvents (*cf.* Section 2.2.6), according to (R = H, alkyl):





The ionization of an ionogen can therefore be regarded as a coordinative interaction between substrate and solvent [281]. The polarization of the covalent bond to be ionized can occur *via* a nucleophilic attack of the EPD solvent on the electropositive end of the bond, or by an electrophilic attack of an EPA solvent on the electronegative end. Both attacks can, of course, also occur simultaneously. The following examples are illustrative.

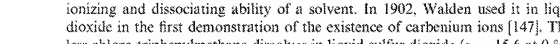


In EPD solvents, ionization depends on the stabilization of the cation through coordination and, in some solvents, on solvation of the anions as well. In EPA solvents, the anion is stabilized through coordination and, to a lesser extent, additional solvation of the cation may occur.

An evaluation of the ionizing power of a solvent requires knowledge, not only of its coordinating abilities, but also of its relative permittivity. According to Eq. (2-13), solvents of high relative permittivity promote the dissociation of ion pairs. The consequential decrease in ion pair concentration displaces the ionization equilibrium in such a way that new ion pairs are formed from the substrate. Thus, a good ionizing solvent must not only be a good EPD or EPA solvent but also possess a high relative permittivity. The donor and acceptor properties of ionizing solvents can be described empirically in a quantitative way by donor numbers [67] or acceptor numbers [70] (*cf.* Section 2.2.6).

The extraordinary ionizing ability of water is above all due to the fact that it may act as an EPD as well as an EPA solvent. Thus, water is both an ionizing and dissociating medium whereas nitromethane, nitrobenzene, acetonitrile, and sulfolane are mainly dissociating. *N*,*N*-Dimethylformamide, dimethyl sulfoxide, and pyridine are mildly dissociating but good ionizing solvents. Hexamethylphosphoric triamide is an excellent ionizing medium due to its exceptional donor properties, particularly in the case of metal-carbon bonds [145, 146]. Alcohols and carboxylic acids, as hydrogen-bond donors are good EPA solvents and, therefore, good ionizing solvents for suitable substrates.

Chloro-triphenylmethane constitutes a classical example for distinguishing the ionizing and dissociating ability of a solvent. In 1902, Walden used it in liquid sulfur dioxide in the first demonstration of the existence of carbenium ions [147]. The colourless chloro-triphenylmethane dissolves in liquid sulfur dioxide ($\varepsilon_r = 15.6$ at 0 °C), giving an intense yellow colour ($\lambda_{max} = 430$ nm). This is caused by a partial formation of ion pairs, which do not conduct electricity. At low concentrations, the ion pairs partially dissociate into free ions, which do conduct electricity [148, 149].



(2-18)

$K_{ion} = 1.46 \cdot 10^{-2}$ (0 °C); $K_{Dissoc} = 2.88 \cdot 10^{-3}$ mol/L (0 °C);

$K_{exp} = 4.1 \cdot 10^{-5}$ mol/L (0 °C) [148].

Table 2-11. Ionization equilibrium constants K_{Ion} of chloro-triphenylmethane in various solvents at 0 ... 25 °C [150]. *Cf.* also [282].

Solvents	ε_r[a] (at 0 ... 25 °C)	$K_{Ion} \cdot 10^4$	References
Nitrobenzene	34.8 (25 °C)	Too low to measure (25 °C)[c]	[151]
Acetonitrile	35.9 (25 °C)	Too low to measure (25 °C)	[152]
Dichloromethane	8.9 (25 °C)	0.07	[153]
1,1,2,2-Tetrachloroethane	8.2 (20 °C)	0.48 (18.5 °C)	[154]
1,2-Dichloroethane	10.4 (25 °C)	0.56 (20 °C)	[154]
Nitromethane	35.9 (25 °C)	2.7 (25 °C)	[155]
Sulfur dioxide	15.6 (0 °C)[b]	146 (0 °C)	[148]
Formic acid	58.5 (16 °C)	3100 (20.5 °C)	[156]
m-Cresol	11.8 (25 °C)	5600[d] (18 °C)	[157]

[a] J. A. Riddick, W. B. Bunger, and T. K. Sakano: *Organic Solvents*, 4th edition, in A. Weissberger (ed.), *Techniques of Chemistry*, Vol. II, Wiley-Interscience, New York, 1986.
[b] A. A. Maryott and E. R. Smith: *Table of Dielectric Constants of Pure Liquids*, NBS Circular 514, Washington, 1951.
[c] Because nitrobenzene absorbs strongly at the wavelength of the carbenium ion maximum from chlorotriphenylmethane, this result was obtained with chloro-diphenyl-4-tolylmethane.
[d] This K_{Ion} value corresponds to 36 ± 4% ionization of chlorotriphenylmethane in *m*-cresol [157].

Sulfur dioxide is a π-electron-pair acceptor. The standard explanation for the strong ionizing power of SO_2 is the formation of an EPD—EPA complex between the halide anion and the sulfur dioxide molecules [148]. Table 2-11 summarizes some of the available data concerning the comparative efficiencies of various solvents in promoting the ionization of chloro-triphenylmethane [150].

The K_{Ion} of chloro-triphenylmethane varies in different solvents by at least a factor of 10^5. In the protic solvents *m*-cresol and formic acid, which have relative permittivities of 11.8 and 58.5, respectively, chloro-triphenylmethane is strongly ionized but is only slightly dissociated in the former. The remarkable ionizing power of phenols and carboxylic acids has been attributed to their EPA properties, *i.e.* their ability to form a hydrogen bond between the hydroxyl group and the halide ion. Solvents with high relative permittivities but lacking pronounced EPA properties, such as acetonitrile and nitrobenzene, are barely capable of ionizing chloro-triphenylmethane. In the case of tri(4-anisyl)-chloromethane, the K_{Ion} value in the EPA solvent sulfur dioxide at 0 °C is about $5 \cdot 10^{10}$ times greater than that in nitrobenzene at 25 °C [151].

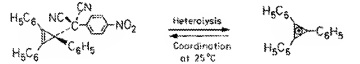
On the other hand, the ionization of chloro-triphenylmethane is also favored by EPD solvents. Since the developing carbenium ion is an electrophilic species, it readily interacts with nucleophilic solvents. Thus, the extent of ionization of chloro-triphenylmethane in nitrobenzene increases on the addition of aprotic EPD solvents in direct relation to the donor number [158]. See reference [299] for a study of ionization and dissociation equilibria of other halo-triphenylmethanes in solution ($Ph_3C—X$ with X = F, Cl, Br).

Another remarkable example of the solvent effect on the ionization of ionogens is the Friedel-Crafts intermediate antimony pentachloride/4-toluoyl chloride. It can exist as two distinct well-defined adducts depending on the solvent from which it is recrystallized, the donor-acceptor complex *(2)* or the ionic salt *(3)* [159].

(2) (3)

The donor-acceptor complex *(2)* is isolated from tetrachloromethane solution ($\varepsilon_r = 2.2$), the ionic salt *(3)* from chloroform solution ($\varepsilon_r = 4.9$). When dissolved in chloroform, the donor-acceptor complex recrystallizes as the ionic salt. Similarly, the ionic salt is converted to the donor-acceptor complex when dissolved in tetrachloromethane. This result shows that in solution an equilibrium exists between the two forms. The isolation depends on the solvent used for recrystallization. Similar results have been obtained in the case of the adduct between acetyl chloride and aluminium trichloride, which is un-ionized in chloroform, but completely ionized in nitrobenzene [160].

Other nice examples of well-studied solvent-dependent ionization equilibria of ionogens are azidocycloheptatriene $\rightleftharpoons$ tropylium azide [282, 283] and (triphenylcyclopropen-1-yl) (4-nitrophenyl)malononitrile *(2a)* $\rightleftharpoons$ triphenylcyclopropenium dicyano(4-nitrophenyl)methide *(3a)*, the latter being one of the first examples of direct heterolysis of a weak carbon-carbon bond to a carbocation and carbanion in solution [284].



(2a) (3a)

When dissolved in nonpolar solvents such as benzene or diethyl ether, the colourless *(2a)* forms an equally colourless solution. However, in more polar solvents (*e.g.* acetone, acetonitrile), the deep-red colour of the resonance-stabilized carbanion of *(3a)* appears ($\lambda = 475 \ldots 490$ nm), and its intensity increases with increasing solvent polarity. The carbon-carbon bond in *(2a)* can be broken merely by changing from a less polar to a more polar solvent. Cation and anion solvation provides the driving force for this heterolysis reaction, whereas solvent displacement is reqnired for the reverse coordination reaction. The Gibbs energy for the heterolysis of *(2a)* correlates well with the reciprocal solvent relative permittivity in accordance with the Born electrostatic equation [285], except for EPD solvents such as dimethyl sulfoxide, which give larger $\Delta G^{\circ}_{\text{het}}$ values than would be expected for a purely electrostatic solvation [284].

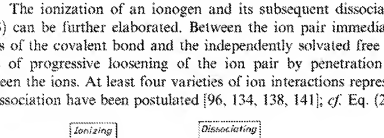
The first purely organic salt, $C_{48}H_{51}^{\oplus}C_{67}H_{39}^{\ominus}$, consisting solely of carbon and hydrogen atoms and being fully ionised in the crystalline state and in solution, was prepared by mixing tris[1-(5-isopropyl-3,8-dimethylazulenyl)]cyclopropenylium perchlorate with potassium tris(7*H*-dibenzo[*c,g*]fluorenylidenemethyl)methide (Kuhn's anion) in tetrahydrofuran solution [292]. An analogous green hydrocarbon salt, $C_{12}H_{15}^{\oplus}$ $C_{67}H_{39}^{\ominus}$, which consists of the tri(cyclopropyl)cyclopropenylium cation and Kuhn's anion, is completely ionized in the solid and in DMSO solution. However, in chloroform, tetrachloromethane, and benzene solutions at room temperature, a covalent hydrocarbon is formed from the two ions. Surprisingly, cooling the chloroform solution to -78 °C or evaporation of the solvent regenerates the original green hydrocarbon salt.

In acetonitrile, the ionic and covalent forms coexist in a clean equilibrium. This compound is the first hydrocarbon that only exists covalently in solution [292]. In acetone, dichloromethane, and tetrahydrofuran, a radical, derived from Kuhn's anion by single-electron transfer (SET), was detected in addition to the two ionic species. Thus, all three types of elementary organic species (ion, radical, and a covalent compound) are shown to be able to coexist in a solution equilibrium, depending on the solvent used [292]. For reviews on solvent-dependent equilibria, including radical pairs (produced by bond heterolysis) and radical ion pairs (produced by electron transfer), see references [291, 400, 401].

Another type of ion pairs, called *penetrated ion pairs* [402], has been found by studying the conductivity of tetraalkylammonium tetrafluoroborates (with variable alkyl-chain lengths) [399, 403], and the UV/Vis spectroscopic behaviour of salts with a trimethinium cyanine cation and the tetrakis(phenylethynyl)borate anion [404], in non-dissociating solvents of low relative permittivity. Clearly, in solutions of such low relative permittivity any ionic species will be highly associated. However, it has been found that the ion pairs formed can be smaller than the sum of the van der Waals radii of the components. Clearly, the ions of the ion pair interpenetrate each other depending on their molecular structure: in the first case, the BF_4^- ion penetrates into the voids between the alkyl chains of the tetraalkylammonium ion, and in the second case the cyanine cation penetrates into the crevices of the borate ion.

It should be mentioned that the ionization step in Eq. (2-13) is analogous to that involved in S_N1 and S_N2 reactions of aliphatic substrates. For example, in solvolytic reactions of haloalkanes, the process of going from a covalently bonded initial state to a dipolar or ionic activated complex (transition state) is similar to the ionization step in Eq. (2-13). Therefore, those solvent properties that promote ionization are also important in the estimation of solvent effects on nucleophilic displacement reactions [161] (*cf.* Section 5.4.1).

The ionization of an ionogen and its subsequent dissociation according to Eq. (2-13) can be further elaborated. Between the ion pair immediately formed on heterolysis of the covalent bond and the independently solvated free ions, there are several steps of progressive loosening of the ion pair by penetration of solvent molecules between the ions. At least four varieties of ion interactions representing different stages of dissociation have been postulated [96, 134, 138, 141]; *cf.* Eq. (2-19) and Fig. 2-14.



$$\{A\text{-}B\}_{solv} \rightleftharpoons \{A^{\oplus}B^{\ominus}\}_{solv} \rightleftharpoons \{A^{\oplus}\,//\,B^{\ominus}\}_{solv} \rightleftharpoons \{A^{\oplus}\}_{solv} + \{B^{\ominus}\}_{solv} \qquad (2\text{-}19)$$

Based on the mutual geometric arrangement of the two ions and the solvent molecules, the following definitions of ion pairs have been given (*cf.* Fig. 2-14).

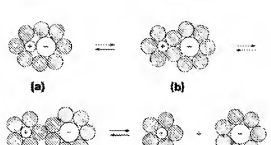


Fig. 2-14. Schematic representation of the equilibrium between (a) a solvated contact ion pair, (b) a solvent-shared ion pair, (c) a solvent-separated ion pair, and (d) unpaired solvated ions of a 1:1 ionophore in solution, according to reference [241]. Hatched circles represent solvent molecules of the primary solvation shell.

First, immediately after ionization, *contact ion pairs**) are formed, in which no solvent molecules intervene between the two ions that are in close contact. The contact ion pair constitutes an electric dipole having only one common primary solvation shell. The ion pair separated by the thickness of only one solvent molecule is called a *solvent-shared ion pair**). In solvent-shared ion pairs, the two ions already have their own primary solvation shells. These, however, interpenetrate each other. Contact and solvent-shared ion pairs are separated by an energy barrier which corresponds to the necessity of creating a void between the ions that grows to molecular size before a solvent molecule can occupy it. Further dissociation leads to *solvent-separated ion pairs**). Here, the primary solvation shells of the two ions are in contact, so that some overlap of secondary and further solvation shells takes place. Increase in ion-solvating power and relative permittivity of the solvent favours solvent-shared and solvent-separated ion pairs. However, a clear experimental distinction between solvent-shared and solvent-separated ion pairs is not easily obtainable. Therefore, the designations solvent-shared and solvent-separated ion pairs are sometimes interchangeable. Eventually, further dissociation of the two ions leads to *free, i.e.* unpaired solvated *ions* with independent primary and secondary solvation shells. The circumstances under which contact, solvent-shared, and solvent-separated ion pairs can exist as thermodynamically distinct species in solution have been reviewed by Swarcz [138] and by Marcus [241].

Interestingly, theoretical calculations of Gibbs energy profiles for the separation of *tert*-butyl cation and chloride ion during the hydrolysis of 2-chloro-2-methylpropane have given support for the existence of a contact ion pair, while solvent-separated ion pairs and free, unpaired ions do not appear as energetically distinct species [302]. Monte Carlo simulations predict the occurrence of a contact ion pair at a C—Cl distance of 290 pm and the onset of the solvent-separated ion pair regime near 550 pm (*cf.* the normal C····Cl bond length of ca. 180 pm). A significant barrier of ca. 8 kJ/mol (2 kcal/mol) between the contact and solvent-separated ion pairs has been calculated [302]. For tetramethylammonium chloride in dilute aqueous solution at 25 °C, the contact and

* Some authors use the designations *intimate ion pair*, *internal ion pair* (Winstein [162]), *cage ion pair* (Kosower [129]), or *inner-sphere ion pair* (Marcus [241]) instead of *contact ion pair*, and *external ion pair* (Winstein [162]) or *outer-sphere ion pair* (Marcus [241]) for *solvent-shared* and *solvent-separated ion pairs*. The more general designation *tight* and *loose ion pair* (Swarcz [138]) implies that, in principle, more than two different kinds of ion pairs may exist in solution. An IUPAC glossary recommends the designations *tight ion pair* (or *intimate* or *contact ion pair*) and *loose ion pair* [286].

solvent-separated ion pairs are separated by a calculated activation barrier of only 2.9 kJ/mol (0.7 kcal/mol) [302]. Analogous Monte Carlo simulations for sodium iodide ion pairs in water clusters substantiate the existence of distinct contact and solvent-separated ion pairs, showing that the $Na^+ I^-$ contact ion pair is quite stable with respect to dissociation into free ions [405].

The suggestion that ion pairs may exist in more than one distinct form was made by Winstein [162] and by Fuoss [163] in 1954, but direct evidence for the existence of contact and solvent-separated ion pairs came from UV/Vis spectroscopic investigations of sodium fluorenide in tetrahydrofuran solution [141, 164]. Further evidence for the existence of a dynamic equilibrium between contact and solvent-separated ion pairs (*e.g.* hyperfine splitting of radical-anion ESR lines by cationic nuclei; electronic spectra of mesomeric anions; *etc.*) has been summarized by Gordon [96], Szwarc [138], and Marcus [241]. Increasing association of ions in solution greatly affects their chemical behaviour. A large variety of possible ion-pair effects on rate constants, mechanism and stereochemistry is known, especially in reactions of ion pairs containing carbenium ions [161, 165] or carbanions [166, 168, 168a].

The observation that the rate of loss of optical activity during the solvolysis of certain chiral substrates $R^{\delta\oplus} - X^{\delta\ominus}$ exceeded the rate of acid production and the occurrence of a special salt effect led to the postulation of two distinct ion-pair intermediates [161, 162]. The basic Winstein solvolysis scheme is given by Eq. (2-20).

$$\begin{array}{ccccccc} {}^{\delta\oplus}(R{-}X^{\delta\ominus})_{solv} & \rightleftharpoons & (R^{\oplus}\,X^{\ominus})_{solv} & \rightleftharpoons & (R^{\oplus}/\!/\,X^{\ominus})_{solv} & \rightleftharpoons & (R^{\oplus})_{solv} + (X^{\ominus})_{solv} \\ & & \downarrow & & \downarrow & & \downarrow \\ & & \text{products} & & \text{products} & & \text{products} \end{array} \qquad (2\text{-}20)$$

According to this scheme, the solvolysis products are not only obtained from free unpaired ions, but also from the two different ion pairs, depending on the solvent-dependent degree of dissociation.

An analogous scheme holds for the reactions of certain dipolar organometallics $R^{\delta\ominus} - M^{\delta\oplus}$, according to Eq. (2-21) [138, 167, 168, 168a].

$$\begin{array}{lllll} {}^{\delta\ominus\ \delta\oplus}(R{-}M)_{n,solv} & \rightleftharpoons & {}^{\delta\ominus\ \delta\oplus}(R{-}M)_{solv} & \rightleftharpoons & (R^{\ominus}M^{\oplus})_{solv} \\ \text{Higher Aggregates} & & \text{Ionogen} & & \text{Contact Ion Pair} \end{array}$$

$$\rightleftharpoons (R^{\ominus}/\!/\,M^{\oplus})_{solv} \rightleftharpoons (R^{\ominus})_{solv} + (M^{\oplus})_{solv} \qquad (2\text{-}21)$$

Solvent-separated Ion Pair — Free Ions

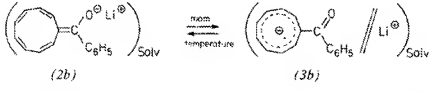
Whereas the spectral behavior of solvent-separated ion pairs and free ions is very similar, the UV/Vis spectra of contact and solvent-separated ion pairs are usually different from each other, as has been shown with sodium fluorenide [141, 164]. Due to the penetration of solvent molecules between the ion-pair couples, the direct influence of the metal cation on the π-electron system of the carbanion is lost. With increasing dissociation, the absorption maximum of sodium fluorenide in tetrahydrofuran solution is shifted bathochromically in the direction of the absorption maximum of the free

fluorenide ion: $\lambda_{max} = 356$ nm $\rightarrow$ 373 nm $\rightarrow$ 374 nm, for the contact ion pairs, solvent-separated ion pairs, and free fluorenide ions, respectively [164]. The equilibrium between contact and solvent-separated ion pairs is shifted in the direction of increased dissociation by the addition of cation solvators such as EPD solvents. Thus, the proportion of solvent-separated ion pairs for sodium fluorenide at 25 °C in tetrahydrofuran is 5 cmol/mol, whereas in 1,2-dimethoxyethane, a better cation solvator, it is 95 cmol/mol. In strong EPD solvents such as dimethyl sulfoxide, hexamethylphosphoric triamide, or polyetheleneglycol dimethyl ethers, most of the fluorenide salt exists as solvent-separated ion pairs only. Small quantities of dimethyl sulfoxide, when added to the sodium fluorenide solution in 1,4-dioxane, convert the contact ion pairs to dimethyl sulfoxide-separated ion pairs [141, 164].

Sodium naphthalenide behaves similarly when the solvent is changed from tetrahydrofuran to 1,2-dimethoxyethane. The formation of solvent-separated from contact ion pairs is shown by a dramatic simplification of the ESR spectrum: the 100-line spectrum of the contact ion pair, due to the spin-spin coupling of the unpaired electron with the four equal hydrogen nuclei in the α- and β-positions, together with the sodium nucleus ($I = 3/2$), collapses to a 25-line spectrum as the interaction with the sodium ion is disrupted [169, 170].

Other illustrative examples of carbanionic ion-pair dissociation/aggregation are: lithium triphenylmethide, which exists as a tight ion pair in diethyl ether and as a solvent-separated ion pair in tetrahydrofuran, as shown by UV/Vis spectrophotometric measurements [287], and lithium 10-phenylnonafulvene-10-oxide, which exists as a tight ion pair *(2b)* in tetrahydrofuran solution and as a solvent-separated ion pair *(3b)* when hexamethylphosphoric triamide or dimethyl sulfoxide are added (^{1}H and ^{13}C NMR measurements) [288].

This second case is particularly interesting since the addition of an EPD solvent is connected with a shift from the olefinic nonafulvenoxide anion in *(2b)* to the aromatic benzoyl [9] annulene anion in *(3b)*. Without association of the lithium cation with the enolate oxygen atom, the negative charge is preferably delocalized in the [9] annulene ring. Therefore, the aromatic character of this ionophore depends on its ion-pair character [288].



(2b) *(3b)*

The degree of aggregation of organolithium compounds (alkyl-, aryl-, and alkynyl-lithium compounds as well as lithium enolates) in dilute tetrahydrofuran solution at -108 °C has been determined by means of cryoscopic [289] and NMR spectroscopic measurements [290]; for a review on the solution structure of lithium enolates and phenolates, see reference [406].

The enolate and iminate ions of tetra-*n*-butylammonium salts of carbonyl compounds (*e.g.* malonates) and nitriles (*e.g.* 2-phenylpropionitrile) exhibit special dimeric molecular structures in the solid state and in solution (benzene), held together by multi-

ple C—H···O and C—H···N hydrogen bonds, resp., with the α-methylene units of the $(n\text{-Bu})_4N^+$ cation. Thus, these anions are not truly 'naked' carbanions; they interact with one another through hydrogen bonds in a highly ordered manner, leading to another type of ion pairs, called *supramolecular ion pairs* [407]. For a review on genuine non-coordinating anions, see reference [408].

Of particular interest for regio- and stereoselective C—C bond-forming synthetic reactions are lithium organocuprates, the detailed molecular structure of which was unknown for a long time. Application of sophisticated NMR techniques has shown that a representative salt-containing lithium dimethylcuprate, $Me_2CuLi \cdot LiCN$, exists in solution (S = THF, Et_2O) in an equilibrium between homo-dimeric contact ion pairs and monomeric solvent-separated ion pairs such as $[LiS_4]^+$ $[Me—Cu—Me]^-$ [409]. A systematic X-ray study of solid-state structures of lithium organocuprates has substantiated the formation of monomeric solvent-separated ion pairs in good-solvating solvents for Li^+ (*e.g.* THF, crown ethers, amines), while in poor-solvating solvents for Li^+ (*e.g.* Et_2O, Me_2S) a dimeric contact ion pair is found. This is of practical relevance because it seems to be only the lithium organocuprate dimer of the contact-ion type that undergoes C—C bond-forming reactions such as addition to enones [409].

The ^{7}Li NMR spectra of solutions of the dilithium salts of the (*R*)- and (*S*)-configured (*sec*-butoxy)cyclooctatetraene dianion, $Li_2^+[C_8H_7—OC_4H_9]^{3-}$, in the chiral solvent 1,4-bis(dimethylamino)-2,3-dimethoxybutane (DDB; see Table A-2 in the Appendix) were found to be remarkably different. The chiral dilithium salt exists in DDB solution as a mixture of contact and solvent-separated ion pairs. Interestingly, the relative concentration of the contact ion pair is much greater for the (*R*)-enantiomer of $[C_8H_7—OC_4H_9]^{2-}$ than for the (*S*)-enantiomer, indicating a solvent/ion-pair chiral recognition. Thus, the interaction between the chiral solvent and the (*R*)- and (*S*)-*sec*-butoxy groups results in the DDB solvent being more capable of partially separating Li^+ from the (*S*)-enantiomer of $[C_8H_7—OC_4H_9]^{2-}$ than from the (*R*)-enantiomer [410].